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(54) Title: METHODS AND COMPOSITIONS FOR TREATING CARDIOVASCULAR DISEASE USING 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of cardiovascular disease, including, but not limited to, atherosclerosis, reperfusion injury, hypertension, restenosis, arterial inflammation, heart failure, thrombosis and endothelial cell disorders. Specifically, the present invention identifies the differential expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 and 6585 genes in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, and/or in response to manipulations relevant to cardiovascular disease. The present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to conditions. The invention also provides methods for identifying a compound capable of modulating cardiovascular disease. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease.

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METHODS AND COMPOSITIONS FOR TREATING CARDIOVASCULAR DISEASE USING 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 26156, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 OR 6585 MOLECULES

Related Applications

[0001] The present application claims the benefit of U.S. Provisional Application serial No.60/353,224, filed on February 1, 2002, of U.S. Provisional Application serial No.60/364,529, filed on March 15, 2002, of U.S. Provisional Application serial No.60/373,861, filed on April 19, 2002, of U.S. Provisional Application serial No.60/376,287, filed on April 29, 2002, of U.S. Provisional Application serial No.60/388,080, filed on June 12, 2002, of U.S. Provisional Application serial No.60/390,971, filed on June 24, 2002, of U.S. Provisional Application serial No.60/394,130, filed on July 3, 2002, of U.S. Provisional Application serial No.60/394,797 filed on July 10, 2002, of U.S. Provisional Application serial No.60/404,904, filed on August 21, 2002, of U.S. Provisional Application serial No.60/405,450, filed on August 23, 2002, of U.S. Provisional Application serial No.60/408,070, filed on September 4, 2002, of U.S. Provisional Application serial No.60/424,300, filed on November 6, 2002, of U.S. Provisional Application serial No.60/431,079, filed on December 5, 2002, and of U.S. Provisional Application serial No.60/431,042, filed on December 5, 2002. The entire contents of these provisional patent applications are hereby incorporated by this reference.

Background of the Invention

[0002] Cardiovascular disease is a major health risk throughout the industrialized world. Atherosclerosis, the most prevalent of cardiovascular diseases, is the principal cause of heart attack, stroke, and peripheral vascular disease resulting in significant disability and limb loss, and thereby the principle cause of death in the United States.

[0003] Atherosclerosis is a complex disease involving aspects of lipid metabolism and vascular inflammation. Both have significant effects on the initiation and progression of atherosclerosis. Irregular lipid metabolism is a very well established risk factor for atherosclerosis. Elevated low density lipoprotein (LDL), very low density lipoproteins (VLDL), triglycerides and low levels of high density lipoproteins (HDL) all independently contribute to atherosclerosis

development and/or progression. There are a number of effective therapies currently being utilized in the clinic that result in lowering of these risk factors and, in turn decrease the rate of mortality and morbidity associated with atherosclerotic disease. Some of these therapies include the cholesterol lowering drugs statins, the triglyceride lowering drugs fibrates and niacin and the triglyceride lowering/HDL raising PPAR alpha activators. There is a need to identify new targets for atherosclerosis therapy.

[0004] There have been significant advances made in understanding the role that inflammation plays in the process of atherosclerosis. Atherosclerosis involves many cell types and molecular factors (described in, for example, Ross (1993) *Nature* 362: 801-809).

The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. Injury or dysfunction of the vascular endothelium is a common feature of many conditions that predispose an individual to accelerated development of atherosclerotic cardiovascular disease. There has been considerable effort in establishing that hypertension contributes to atherosclerosis. The identification of molecules that regulate blood pressure and vascular tone will be useful in discovering new therapies to treat cardiovascular diseases such as atherosclerosis.

Detailed Description of the Invention

[0005] The present invention provides methods and compositions for the diagnosis and treatment of cardiovascular disease. As used herein, disorders involving the heart, or "cardiovascular disease" or a "cardiovascular disorder" include a disease or disorder which affects the cardiovascular system, e.g., the heart, the blood vessels, and/or the blood. A cardiovascular disorder can be caused by an imbalance in arterial pressure, a malfunction of the heart, or an occlusion of a blood vessel, e.g., by a thrombus. A cardiovascular disorder includes, but is not limited to disorders such as arteriosclerosis, atherosclerosis, cardiac hypertrophy, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, valvular disease, including but not limited to, valvular degeneration caused by calcification, rheumatic heart disease, endocarditis, or

complications of artificial valves; atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, pericardial disease, including but not limited to, pericardial effusion and pericarditis; cardiomyopathies, *e.g.*, dilated cardiomyopathy or idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, ischemic disease, arrhythmia, sudden cardiac death, and cardiovascular developmental disorders (*e.g.*, arteriovenous malformations, arteriovenous fistulae, raynaud's syndrome, neurogenic thoracic outlet syndrome, causalgia/reflex sympathetic dystrophy, hemangioma, aneurysm, cavernous angioma, aortic valve stenosis, atrial septal defects, atrioventricular canal, coarctation of the aorta, ebsteins anomaly, hypoplastic left heart syndrome, interruption of the aortic arch, mitral valve prolapse, ductus arteriosus, patent foramen ovale, partial anomalous pulmonary venous return, pulmonary atresia with ventricular septal defect, pulmonary atresia without ventricular septal defect, persistence of the fetal circulation, pulmonary valve stenosis, single ventricle, total anomalous pulmonary venous return, transposition of the great vessels, tricuspid atresia, truncus arteriosus, ventricular septal defects). A cardiovascular disease or disorder also can include an endothelial cell disorder.

[0006] As used herein, an "endothelial cell disorder" includes a disorder characterized by aberrant, unregulated, or unwanted endothelial cell activity, *e.g.*, proliferation, migration, angiogenesis, or vascularization; or aberrant expression of cell surface adhesion molecules or genes associated with angiogenesis, *e.g.*, TIE-2, FLT and FLK. Endothelial cell disorders include tumorigenesis, tumor metastasis, psoriasis, diabetic retinopathy, endometriosis, Grave's disease, ischemic disease (*e.g.*, atherosclerosis), and chronic inflammatory diseases (*e.g.*, rheumatoid arthritis).

[0007] A cardiovascular disease can also include thrombosis. Thrombosis can result from platelet dysfunction, *e.g.* seen in myocardial infarction, angina, hypertension, lipid disorders, diabetes mellitus; myelodysplastic syndromes; myeloproliferative syndromes (including polycythemia vera and thrombocythemia); thrombotic thrombocytopenic purpuras; HIV-induced platelet disorders (AIDS-Thrombocytopenia); heparin induced thrombocytopenia; mural cell alterations/interactions leading to platelet aggregation/degranulation, vascular endothelial cell activation/injury, monocyte/macrophage extravasation and smooth muscle cell proliferation; autoimmune disorders such as, but not limited to vasculitis, antiphospholipid syndromes, systemic lupus erythromatosis; inflammatory diseases, such as, but not limited to immune activation; graft Vs host disease; radiation induced hypercoagulation; clotting factor dysregulation

either hereditary (autosomal dominant or recessive) such as, but not limited to clotting factor pathways including protein C/S, Anti-thrombin III deficiency, and the Factor V Leiden mutation or acquired such as but not limited to autoimmune, cancer -associated and drug-induced dysregulation of clotting factors.

5 [0008] "Treatment", as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or
10 affecting the disease or disorder, at least one symptom of disease or disorder or the predisposition toward a disease or disorder. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Representative molecules are described herein.

[0009] The present invention is based, at least in part, on the discovery that nucleic
15 acid and protein molecules, (described infra), are differentially expressed in cardiovascular disease states relative to their expression in normal, or non-cardiovascular disease states. The modulators of the molecules of the present invention, identified according to the methods of the invention can be used to modulate (*e.g.*, inhibit, treat, or prevent) or diagnose cardiovascular disease, including, but not limited to, atherosclerosis and
20 thrombosis.

[0010] "Differential expression", as used herein, includes both quantitative as well as qualitative differences in the temporal and/or tissue expression pattern of a gene. Thus, a differentially expressed gene may have its expression activated or inactivated in normal versus cardiovascular disease conditions (for example, in an experimental cardiovascular
25 disease system such as in an animal model for atherosclerosis). The degree to which expression differs in normal versus cardiovascular disease or control versus experimental states need only be large enough to be visualized via standard characterization techniques, *e.g.*, quantitative PCR, Northern analysis, subtractive hybridization. The expression pattern of a differentially expressed gene may be used as part of a prognostic or diagnostic
30 cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis, evaluation, or may be used in methods for identifying compounds useful for the treatment of cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis. In addition, a differentially expressed gene involved in cardiovascular disease may represent a target gene such that modulation of the level of target gene expression or of target gene product activity will act to cure, heal,

alleviate, relieve, alter, remedy, ameliorate, improve or affect a cardiovascular disease condition, *e.g.*, atherosclerosis and/or thrombosis. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of cardiovascular disease. Although the genes described herein may be differentially
5 expressed with respect to cardiovascular disease, and/or their products may interact with gene products important to cardiovascular disease, the genes may also be involved in mechanisms important to additional cardiovascular cell processes.

Molecules of the Present Invention

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Gene ID 1682

[0011] The human 1682 sequence (SEQ ID NO:1), (GI:340010), known also as human dual specificity protein kinase (TTK or PYT), is approximately 3866 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid
15 1026 to 3551 of SEQ ID NO:1, encodes a 841 amino acid protein (SEQ ID NO: 2) (GI:340011).

[0012] As assessed by TaqMan analysis, 1682 mRNA expression was detected in megakaryocytic and erythroid lineages *in vitro* and in bone marrow megakaryocytes (CD41+ cells). Little or no 1682 mRNA expression was observed in the major human
20 organs, *i.e.*, heart, lung, liver, kidney and spleen. Higher levels of 1682 mRNA was observed in the platelets of patients with acute coronary syndromes (myocardial infarct and unstable angina) that also have a history of diabetes as compared with platelets from patients with no history of diabetes and also with normal, age-matched, volunteers.

[0013] Signal transduction via serine/threonine and/or tyrosine kinases has been
25 implicated in platelet reactivity, a key component of thrombosis associated with acute coronary syndromes [Circulation. 2000. 102(16):1924-1930]. Evidence exists suggesting that the platelets of diabetic patients are more reactive than normal platelets [Thrombosis Research. 1998. 90(4):181-90]. 1682 is stimulated by the cytokine tumor necrosis factor (TNF) [Cytokine. 2000. 12(2):142-150], and elevated serum TNF levels occur in patients
30 with diabetes. Collectively, these data indicate that the increased TNF levels in diabetic patients stimulate increased 1682 expression, thereby contributing to the platelet reactivity and the acute coronary syndrome. Due to these observations and the expression pattern of 1682 in megakaryocytic and erythroid lineages *in vitro*, modulators of 1682 activity would block platelet reactivity and thus be useful as therapeutics in treating thrombosis and

thrombotic conditions. 1682 polypeptides of the present invention are useful to screen for modulators of 1682 activity

Gene ID 6169

5 [0014] The human 6169 sequence (SEQ ID NO:3), (GI:1930074), known also as C-4 methyl sterol oxidase (DESP4), is approximately 1751 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 27 to 908 of SEQ ID NO:3, encodes a 293 amino acid protein (SEQ ID NO: 4) (GI:1930075).

[0015] As assessed by TaqMan analysis, 6169 mRNA was expressed at high levels
10 in human liver, as compared to other human tissues tested. 6169 mRNA was regulated by cholestyramine in a marmoset model of atherosclerosis. 6169 mRNA was repressed by n-3 polyunsaturated fatty acid in an African Green Monkey model of atherosclerosis.

[0016] 6169 (C-4 methyl sterol oxidase) is the human ortholog of the yeast gene ERG25 which has been implicated in sterol biosynthesis. Inhibition of C-4 methyl sterol
15 oxidase is predicted to reduce total cholesterol and triglycerides. 6169 mRNA expression was repressed by n-3 polyunsaturated (hypolipidemic diet) and also regulated by cholestyramine and exhibits liver enriched expression. Due to the regulation pattern of 6169 marmoset and African green monkey model atherosclerosis, modulators of 6169 activity would be useful in treating cardiovascular diseases including but not limited to
20 atherosclerosis and hypercholesterolemia. 6169 polypeptides are useful in screening for modulators of 6169 activity.

Gene ID 6193

[0017] The human 6193 sequence (SEQ ID NO:5), also known as a GPCR, is
25 approximately 1029 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1 to 1029 of SEQ ID NO:5, encodes a 342 amino acid protein (SEQ ID NO: 6).

[0018] As assessed by TaqMan analysis, 6193 mRNA was expressed in human blood vessels and in vessel-rich organs, the highest expression level seen in skeletal
30 muscle. 6193 mRNA expression was also seen in the vasculature in both endothelial and smooth muscle cells.

[0019] Due to the widespread expression of 6193 in human vasculature, modulators of 6193 activity would modulate vascular tone and thus would be useful in treating cardiovascular disorders, including but not limited to hypertension and those

conditions characterized by hypertension. 6193 polypeptides would be useful in screening for modulators of 6193 activity.

Gene ID 7771

5 **[0020]** The human 7771 sequence (SEQ ID NO:7), (GI:468325), known also as a human phospholipid transfer protein, is approximately 1750 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 88 to 1569 of SEQ ID NO:7, encodes a 493 amino acid protein (SEQ ID NO: 8) (GI:468326).

10 **[0021]** As assessed by TaqMan analysis, 7771 mRNA expression was detected in brain, heart, spleen, placenta, and erythroid and megakaryocytic lineages in vitro. 7771 mRNA was also expressed at highest levels in brain and CD61+ bone marrow megakaryocytes. 7771 mRNA was also detected in platelets from patients with coronary artery disease and at lower levels in platelets from normal volunteers.

15 **[0022]** 7771 protein modulates high density lipoprotein (HDL) particles, converting HDL into larger and smaller particles. Lipoproteins play a critical role in maintaining the phospholipid membrane of platelets and the vessel wall. Lipoproteins are also implicated in maintaining hemostasis and preventing thrombosis. The increased reactivity of platelets from patients with acute coronary diseases results from increased expression of genes such as 7771. Therefore, due to the expression pattern of 7771 in the
20 erythroid and megakaryocytic lineages in vitro and its role in vivo, modulators of 7771 activity would be useful in reducing increased reactivity in the platelets of patients with acute coronary diseases. 7771 polypeptides of the present invention are useful to screen for modulators of 7771 activity.

25 **Gene ID 14395**

30 **[0023]** The human 14395 sequence (SEQ ID NO:9), (GI:10946200), known also as human neuromedin receptor 1 (NMUR1), is approximately 1212 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1 to 1212 of SEQ ID NO:9, encodes a 403 amino acid protein (SEQ ID NO: 10) (GI:10946201).

[0024] As assessed by TaqMan analysis, 14395 mRNA showed restricted expression in an organ recital study. The highest expression of 14395 mRNA was observed in breast, adipose, and pancreas. Medium expression of 14395 mRNA was shown in blood vessels, kidney, liver and prostate. Among cardiovascular rich organs

(heart, kidney, skeletal muscle and liver), 14395 mRNA was expressed in kidney and liver. There is little or no expression in heart and skeletal muscle. 14395 mRNA was also expressed in all veins and some aorta/arteries. In addition, 14395 mRNA was expressed in laser captured vascular smooth muscle cells in vein.

- 5 [0025] Due to the widespread expression of 14395 in human vasculature and kidney, modulators of 14395 activity would modulate vascular tone and thus would be useful in treating cardiovascular disorders, including but not limited to hypertension and those conditions characterized by hypertension. 14395 polypeptides would be useful in screening for modulators of 14395 activity.

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Gene ID 29002

- [0026] The human 29002 sequence (SEQ ID NO:11), known also as a eukaryotic protein kinase, is approximately 2370 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 43 to 1338 of SEQ ID NO:11, encodes
15 a 431 amino acid protein (SEQ ID NO: 12).

- [0027] As assessed by TaqMan analysis, 29002 mRNA was expressed in both in vivo and in vitro samples. 29002 mRNA was expressed in human vasculature. Expression of 29002 mRNA was upregulated in primate atheroma samples compared to normal vessels. In addition, 29002 mRNA was upregulated in macrophages which had been
20 stimulated with CD40 ligand, but not in endothelial cells or smooth muscle cells. In contrast, 29002 mRNA was down-regulated in endothelial cells that were stimulated with mevastatin.

- [0028] Due to the expression pattern of 29002 in the human vasculature, modulation of 29002 would affect atherogenesis and thus be useful as treatment for
25 atherogenesis and atherogenic events. 29002 polypeptides are useful in screening for modulators of 29002 activity.

Gene ID 33216

- [0029] The human 33216 sequence (SEQ ID NO:13), (GI:4768276), known also as
30 a human long-chain acyl-CoA synthetase or fatty acid transport protein 5 (FATP-5), is approximately 2347 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 71 to 2143 of SEQ ID NO:13, encodes a 690 amino acid protein (SEQ ID NO: 14) (GI:4768277).

[0030] As assessed by TaqMan analysis 33216 mRNA was expressed in human liver. Expression of 33216 mRNA in the liver was regulated by statin, in vivo model of African Green Monkey, PPAR alpha agonist (a human hepatocyte model), and regulated by a high cholesterol diet in vivo (African Green Monkey model).

5 [0031] 33216 (FATP-5) is a member of a family of the Fatty Acid Transport Proteins that has been implicated in lipid metabolism. Inhibition of 33216 is predicted to reduce total cholesterol and triglycerides. Therefore, due to 33216 expression pattern in various animal models and its functional role in vivo, modulators of 33216 activity would be useful in treating cardiovascular disorders, including but not limited to atherosclerosis.

10 33216 polypeptides would be useful in screening for modulators of 33216 activity.

Gene ID 43726

[0032] The human 43726 sequence (SEQ ID NO:15), (GI:3176926), known also as galanin 2 receptor homolog, is approximately 1157 nucleotides long including untranslated

15 regions. The coding sequence, located at about nucleic acid 26 to 1132 of SEQ ID NO:15 encodes a 368 amino acid protein (SEQ ID NO:16) (GI:3176927).

[0033] As assessed by TaqMan analysis, 43726 mRNA was expressed in human brain, in megakaryocytic and erythroid lineages in vitro and in bone marrow megakaryocytes (CD61+ cells). 43726 mRNA was also detected in platelets from patients

20 with coronary artery disease but not in platelets from normal volunteers.

[0034] Galinin is a neuropeptide that regulates several neural functions including nociception and cognition through ligation with 3 known receptors, galinin receptors 1-3. The mechanism by which the Gal-3 receptor functions is not known, but evidence suggests a role for galinin and galinin receptors in the regulation of neurotransmitter release [Journal

25 of Biological Chemistry 1998. 273(36):23321-23326]. Due to the expression of 43726 in platelets, and its functional role as the human galanin-3 receptor, it constitutes a parallel pathway may in platelets, implicating 43726 in the control of platelet secretory granule release (degranulation), an important step in thrombus formation. Therefore, modulators of 43726 activity are useful as therapeutics in treating thrombosis and thrombotic

30 conditions. 43726 polypeptides are useful in screening for modulators of 43726 activity.

Gene ID 69292

[0035] The human 69292 sequence (SEQ ID NO:17), (GI:10334989), known also as potassium-dependent Na/Ca exchanger (NCKX3), is approximately 3763 nucleotides

long including untranslated regions. The coding sequence, located at about nucleic acid 38 to 1972 of SEQ ID NO:17, encodes a 644 amino acid protein (SEQ ID NO:18) (GI:14717396).

[0036] 69292 mRNA was detected by TaqMan analysis in human brain, megakaryocyte precursors (CD34+ cells), in megakaryocytes generated in vitro and in CD41+ bone marrow megakaryocytes. 69292 mRNA was found to be present in platelets, with a relative expression higher in platelets from patients with unstable angina and myocardial infraction as compared with platelets from patients with stable angina and normal volunteers.

[0037] Calcium mobilization is a critical component of platelet activation and degranulation. Potassium dependent sodium/calcium exchange activity has been previously demonstrated in platelets [J. Gen. Physiol. 1999. 114:701-711.]. Due to 69292 expression in human brain, megakaryocyte precursors (CD34+ cells), in megakaryocytes generated in vitro and in CD41+ bone marrow megakaryocytes and its functional roles as a sodium/calcium exchanger, 69292 is able to regulate intracellular calcium levels in platelets, thereby regulating platelet reactivity. Modulators of 69292 activity would function to regulate platelet activity and would be useful in treating thrombosis and thrombotic conditions. 69292 polypeptides are useful in screening for modulators of 69292 activity.

Gene ID 26156

[0038] The human 26156 sequence (SEQ ID NO:19), is approximately 1228 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 78 to 728 of SEQ ID NO:19, encodes a 216 amino acid protein (SEQ ID NO:20).

[0039] As assessed by TaqMan analysis, 26156 mRNA was expressed in artery and vein samples. Modulators of 26156 activity are useful in treating cardiovascular diseases. 26156 polypeptides of the present invention are useful in screening for modulators of 26156 activity.

Gene ID 32427

[0040] The human 32427 sequence (SEQ ID NO:21), also known as Acyl co A synthase 5 (ACS 5), is approximately 3371 nucleotides long including untranslated

regions. The coding sequence, located at about nucleic acid 114 to 2333 of SEQ ID NO:21, encodes a 739 amino acid protein (SEQ ID NO:22).

[0041] As assessed by TaqMan analysis, 32427 mRNA was expressed in the human liver. 32427 mRNA was shown to be repressed by cholesterol in monkey liver
5 model. 32427 mRNA was also shown to be up-regulated in human hepatocytes by combination statin/PPAR alpha agonist treatment.

[0042] 32427 is also known as Acyl co A synthase 5 (ACS 5). Inhibition of 32427 or ACS 5 is predicted to reduce total cholesterol and triglycerides. 32427 is repressed by cholesterol and elevated by the hypolipidemic therapeutic combination of statin/fibrate.

10 This pattern is identical to that observed for genes known to be involved in cholesterol metabolism. Therefore, 32427 has a potential role in cholesterol metabolism/biosynthesis. Due to the 32427 expression in the human liver and various animal models, modulators of 32427 activity are useful in treating cardiovascular diseases. 32427 polypeptides of the present invention are useful in screening for modulators of 32427 activity.

Gene ID 2402

[0043] The human 2402 sequence (SEQ ID NO:23), known also as EDG-4 GPCR, is approximately 1734 nucleotides long including untranslated regions. The coding
20 sequence, located at about nucleic acid 85 to 1233 of SEQ ID NO:23, encodes a 382 amino acid protein (SEQ ID NO:24).

[0044] As assessed by TaqMan analysis, 2402 mRNA was expressed in the human liver. 2402 mRNA was also repressed by cerivastatin in a marmoset model. In a human hepatocyte model, 2402 mRNA was also regulated by statin/PPAR alpha agonist in vitro.

[0045] 2402 is also known as EDG-4 GPCR. Regulation of 2402 or EDG-4 is
25 predicted to reduce total cholesterol and triglycerides. 2402 expression is repressed by cerivastatin in a marmoset model which predicts a role in cholesterol metabolism/biosynthesis. Due to 2402 mRNA expression in the human liver and marmoset model, modulators of 2402 activity are useful in treating cardiovascular diseases. 2402 polypeptides of the present invention are useful in screening for modulators
30 of 2402 activity.

Gene ID 7747

[0046] The human 7747 sequence (SEQ ID NO:25), known also as GMP reductase, is approximately 277 nucleotides long including untranslated regions. The

coding sequence, located at about nucleic acid 174 to 260 of SEQ ID NO:25, encodes a 29 amino acid protein (SEQ ID NO: 26).

[0047] As assessed by TaqMan analysis, 7747 mRNA was expressed in the human liver. 7747 mRNA was also repressed by cerivastatin a marmoset model.

- 5 [0048] 7747 is known also as GMP reductase. Regulation of 7747 or GMP reductase is predicted to reduce total cholesterol and triglycerides. 7747 expression is repressed by cerivastatin in a marmoset model which predicts a role in cholesterol metabolism/biosynthesis. Due to 7747 mRNA expression in the human liver and marmoset model, modulators of 7747 activity are useful in treating cardiovascular diseases. 7747
- 10 polypeptides of the present invention are useful in screening for modulators of 7747 activity.

Gene ID 1720

- [0049] The human 1720 sequence (SEQ ID NO:27), known also as ZAP70 kinase, is approximately 3151 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 286 to 2145 of SEQ ID NO:27, encodes a 619 amino acid protein (SEQ ID NO: 28).

- [0050] As assessed by TaqMan expression, 1720 mRNA was expressed in the human liver. 1720 mRNA was also shown to be repressed by fenofibrate in vivo and by
- 20 PPAR alpha selective agonist in vivo.

- [0051] 1720 is also known as ZAP70 kinase. Inhibition of 1720 or ZAP70 kinase is predicted to reduce total cholesterol and triglycerides. 1720 expression is repressed by fenofibrate and a PPAR alpha selective agonist in a marmoset model which predicts a role in triglyceride/cholesterol metabolism. Due to 1720 mRNA expression in the human liver
- 25 and marmoset model, modulators of 1720 activity are useful in treating cardiovascular diseases. 1720 polypeptides of the present invention are useful in screening for modulators of 1720 activity.

Gene ID 9151

- 30 [0052] The human 9151 sequence (SEQ ID NO:29), known also as sorbitol dehydrogenase, is approximately 1808 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 142 to 1215 of SEQ ID NO:29, encodes a 357 amino acid protein (SEQ ID NO:30).

[0053] As assessed by TaqMan analysis, 9151 mRNA was expression in human liver. 9151 mRNA expression was shown to be repressed by statin therapy in vivo, fenofibrate in vivo and PPAR alpha selective agonist in vivo

[0054] 9151 is also known as sorbitol dehydrogenase. Inhibition of 9151 or sorbitol dehydrogenase is predicted protect against the development of atherosclerosis. 9151 mRNA expression is independently repressed by statin, fenofibrate and a PPAR alpha selective agonist in a marmoset model which predicts a role in triglyceride/cholesterol metabolism. Due to 9151 mRNA expression in the human liver and various animal models, modulators of 9151 activity are useful in treating cardiovascular diseases. 9151 polypeptides of the present invention are useful in screening for modulators of 9151 activity.

Gene ID 60491

[0055] The human 60491 sequence (SEQ ID NO:31), known also as a novel glycerol phosphate acytransferase (GPAT), is approximately 2682 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 121 to 2448 of SEQ ID NO:31, encodes a 775 amino acid protein (SEQ ID NO: 32).

[0056] As assessed by TaqMan analysis, 60491 mRNA was expressed in the human liver. 60491 mRNA expression was also repressed by statin therapy and by fenofibrate in vivo.

[0057] 60491 is also known as a novel glycerol phosphate acytransferase (GPAT). Inhibition of 60491, which represents a novel Glycerol Phosphate Acyltransferase (GPAT), is predicted to lower triglyceride and/or cholesterol levels. GPAT's are a class of enzymes that have a demonstrated role in triglyceride metabolism. 60491 mRNA expression is independently repressed by statin, and fenofibrate in a marmoset model, which supports a role in triglyceride/cholesterol metabolism for this gene. Due to 60491 mRNA expression in the human liver and various animal models, modulators of 60491 activity are useful in treating cardiovascular diseases. 60491 polypeptides of the present invention are useful in screening for modulators of 60491 activity.

Gene ID 1371

[0058] The human 1371 sequence (SEQ ID NO:33), known also as tyrosine kinase BMX, is approximately 2604 nucleotides long including untranslated regions. The coding

sequence, located at about nucleic acid 119 to 2212 of SEQ ID NO:33, encodes a 697 amino acid protein (SEQ ID NO: 34).

[0059] As assessed by Taqman analysis, 1371 mRNA was expressed in human vessels and endothelial cells. 1371 mRNA was also shown to be expressed in endothelial cells regulated by PPAR alpha agonist (cardioprotective).

[0060] 1371 is also known as tyrosine kinase BMX. Inhibition of 1371 or BMX kinase is predicted to protect against the development of atherosclerosis. 1371 gene expression is repressed by a PPAR alpha selective agonist in endothelial cells in vitro and 1371 is highly expressed in human arteries (normal and disease), supporting a potential role in the development of atherosclerotic lesions. Due to 1371 mRNA expression in human vessels and endothelial cells, modulators of 1371 activity are useful in treating cardiovascular diseases. 1371 polypeptides of the present invention are useful in screening for modulators of 1371 activity.

Gene ID 7077

[0061] The human 7077 sequence (SEQ ID NO:35), known also as a putative kinase, is approximately 6629 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1 to 6416 of SEQ ID NO:35, encodes a 2080 amino acid protein (SEQ ID NO: 36).

[0062] As assessed by Taqman analysis, 7077 mRNA was expressed in human vessels and endothelial cells. 7077 mRNA was also shown to be expressed in endothelial cells regulated by PPAR alpha agonist (cardioprotective).

[0063] Inhibition of 7077 is predicted to protect against the development of atherosclerosis. 7077 gene expression is repressed by a PPAR alpha selective agonist in endothelial cells in vitro and 7077 is highly expressed in human arteries (normal and disease), supporting a potential role in the development of atherosclerotic lesions. Due to 7077 mRNA expression in human vessels and endothelial cells, modulators of 7077 activity are useful in treating cardiovascular diseases. 7077 polypeptides of the present invention are useful in screening for modulators of 7077 activity.

Gene ID 33207

[0064] The human 33207 sequence (SEQ ID NO:37), known also as a putative novel acyltransferase, is approximately 1945 nucleotides long including untranslated

regions. The coding sequence, located at about nucleic acid 69 to 1802 of SEQ ID NO:37, encodes a 577 amino acid protein (SEQ ID NO:38).

[0065] 33207 gene expression was independently repressed by cerivastatin, fenofibrate and a PPAR alpha selective agonist in a marmoset model.

5 [0066] 33207 is also known as a putative novel acyltransferase. Inhibition of 33207 is predicted to reduce total cholesterol and triglycerides. 33207 gene expression is independently repressed by cerivastatin, fenofibrate and a PPAR alpha selective agonist in a marmoset model which predicts a role in triglyceride/cholesterol metabolism. Due to 33207 mRNA expression in various animal models, modulators of 33207 activity are
10 useful in treating cardiovascular diseases. 33207 polypeptides of the present invention are useful in screening for modulators of 33207 activity.

Gene ID 1419

[0067] The human 1419 sequence (SEQ ID NO:39), known also as ephrin receptor,
15 is approximately 3903 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 712 to 3825 of SEQ ID NO:39, encodes a 1037 amino acid protein (SEQ ID NO:40).

[0068] As assessed by TaqMan analysis, 1419 mRNA was expressed in smooth muscle, vessel and vein.

20 [0069] 1419 is also known as an Ephrin receptor. Inhibition of 1419 is predicted to have beneficial effects in vascular tone/hypertension. 1419 exhibits restricted expression in human smooth muscle cells and human vessel. The expression of 1419 coupled with a potential link to the Rho kinase pathway, known to be involved in vasoactivity, predicts a role for 1419 in vascular tone disease. Due to 1419 mRNA expression in smooth muscle,
25 vessel and vein, modulators of 1419 activity are useful in treating cardiovascular diseases. 1419 polypeptides of the present invention are useful in screening for modulators of 1419 activity.

Gene ID 18036

30 [0070] The human 18036 sequence (SEQ ID NO:41), known also as a calpain 10 protease, is approximately 2180 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 183 to 1736 of SEQ ID NO:41, encodes a 517 amino acid protein (SEQ ID NO:42).

[0071] As determined by TaqMan analysis, 18036 mRNA expression was shown to be upregulated in the brain, kidney and heart. 18036 mRNA was also found to be upregulated in congestive heart failure (CHF) human tissue samples.

[0072] Calpains are cysteine proteases that combine thiol protease activity with calmodulin-like activity. Inhibiting calpain activity leads to attenuated hypoxia-induced cell injury. Increased preload, as seen in pathophysiological states such as heart failure, also induces troponin I degradation independently of myocardial ischemia. Troponin I degradation is a reported marker of myocardial injury in ischemic coronary syndromes. Due to 18036 mRNA expression in the brain, kidney and heart, along with its functional role, modulators of 18036 activity would be useful in treating disorders associated with cardiovascular disease. 18036 polypeptides of the present invention are useful in screening for modulators of 18036 activity.

Gene ID 16105

[0073] The human 16105 sequence (SEQ ID NO:43), known also as a Protein Serine/Threonine Phosphatase family member (PP2C homolog), is approximately 1676 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 391 to 1449 of SEQ ID NO:43, encodes a 352 amino acid protein (SEQ ID NO:44).

[0074] As determined by TaqMan analysis, 16105 mRNA expression was upregulated in heart and brain. Further TaqMan experiments indicated that 16105 was also upregulated in human congestive heart failure tissue and hypertrophied myocytes compared to the normal tissue. In addition, 16105 mRNA was overexpressed in myocytes which attenuated the hypertrophy phenotype. Yeast two-hybrid experiments demonstrated an interaction of 16105 with hsp27 and/or troponin T.

[0075] The hsp27-16105 interaction predicts a role of 16105 in the regulation of actin polymerization which potentially leads to the hypertrophy of myocytes. The troponin T-16105 interaction suggests a role for 16105 in the regulation of the actomyosin ATPase resulting ultimately in a decrease in muscle contraction. Due to 16105 mRNA expression in the brain and heart and its upregulation in congestive heart failure tissue and hypertrophied myocytes, along with its functional role, modulators of 16105 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to congestive heart failure. 16105 polypeptides of the present invention are useful in screening for modulators of 16105 activity.

Gene ID 38650

[0076] The human 38650 sequence (SEQ ID NO:45), known also as an Adenosine Deaminase homolog, is approximately 1680 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 340 to 1407 of SEQ ID NO:45, encodes a 355 amino acid protein (SEQ ID NO:46).

[0077] As determined by TaqMan analysis, the highest expression of 38650 mRNA was found in heart and skeletal muscles. 38650 mRNA expression was also upregulated in human congestive heart failure (CHF) tissue.

[0078] 38650 is 22% identical to known Adenosine Deaminase (ADA). ADA catalyses the conversion of adenosine to inosine. Adenosine plasma levels are higher than normal in CHF patients. The elevation of adenosine is potentially cardioprotective and functions to reduce proinflammatory events. Inhibitors of 38650 would potentially function to increase adenosine levels and decrease TNF-alpha levels in the failing heart. In addition, increased adenosine levels in the blood due to the inhibition of 38650 would potentially stimulate other cardioprotective events such as: the inhibition of the growth of cardiac fibroblasts, vasodilation and reduction of inflammatory processes. Due to 38650 mRNA expression in the heart and skeletal muscles, along with its functional role, modulators of 38650 activity would be useful in treating disorders associated with cardiovascular disease. 38650 polypeptides of the present invention are useful in screening for modulators of 38650 activity.

Gene ID 14245

[0079] The human 14245 sequence (SEQ ID NO:47), known also as Muscle Specific Serine Kinase (MSSK1), is approximately 1835 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 25 to 1626 of SEQ ID NO:47, encodes a 533 amino acid protein (SEQ ID NO:48).

[0080] As determined by TaqMan analysis, 14245 mRNA expression was found to be upregulated in human heart and skeletal muscles. 14245 mRNA was also upregulated in human congestive heart failure tissues.

[0081] 14245 or MSSK1 is homologous to SRPK2 which is a protein kinase found to phosphorylate Ser/Arg rich splicing factors. The potential function of SRPK is in the regulation of pre-mRNA splicing. Several known genes are involved in splicing changes in heart failure tissue samples. These include, but are not limited to, L-type calcium channel

alpha 1c, cardiac troponin T, Fas/Apo1. Thus, 14245 or MSSK1 potentially plays a role in the splicing changes in genes contributing to congestive heart failure. Due to 14245 mRNA expression in the heart and skeletal muscles, along with its functional role, modulators of 14245 activity would be useful in treating disorders associated with cardiovascular disease. 14245 polypeptides of the present invention are useful in screening for modulators of 14245 activity.

Gene ID 58848

[0082] The human 58848 sequence (SEQ ID NO:49), known also as a novel kinase (putative serine/threonine), is approximately 1247 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 44 to 1090 of SEQ ID NO:49, encodes a 348 amino acid protein (SEQ ID NO:50).

[0083] As determined by TaqMan analysis, 58848 mRNA expression was upregulated in human heart tissue and to a lesser degree in skeletal muscle.

[0084] 58848 is a Ser/Thr kinase homologous to a zebrafish kinase and to a Ca/calmodulin dependent protein kinase. Due to 58848 mRNA expression in the heart and skeletal muscles, along with its functional role, modulators of 58848 activity would be useful in treating disorders associated with cardiovascular disease. 58848 polypeptides of the present invention are useful in screening for modulators of 58848 activity.

Gene ID 1870

[0085] The human 1870 sequence (SEQ ID NO:51), known also as GPR22, is approximately 1881 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 237 to 1538 of SEQ ID NO:51, encodes a 433 amino acid protein (SEQ ID NO:52).

[0086] As assessed by TaqMan analysis, 1870 mRNA expression was upregulated in human brain and congestive heart failure tissues. Due to 1870 mRNA expression in the brain and heart tissue, modulators of 1870 activity would be useful in treating disorders associated with cardiovascular disease. 1870 polypeptides of the present invention are useful in screening for modulators of 1870 activity.

Gene ID 25856

[0087] The human 25856 sequence (SEQ ID NO:53), known also as Pyroglutamyl Peptidase (pyrrolidone-carboxylate peptidase), is approximately 1626 nucleotides long

including untranslated regions. The coding sequence, located at about nucleic acid 218 to 808 of SEQ ID NO:53, encodes a 196 amino acid protein (SEQ ID NO:54).

[0088] As assessed by TaqMan analysis, 25856 mRNA was expressed in skeletal muscle and was regulated in human congestive heart failure tissue (CHF).

5 [0089] 25856 is a pyrrolidone-carboxylate pyroglutamyl peptidase (Pcp) type I. Type I pyroglutamyl peptidases are cytosolic proteins. They are involved in removing 5-oxoproline from various penultimate amino acid residues except L-Proline. Due to 25856 mRNA expression in the heart and skeletal muscles, along with its functional role, modulators of 25856 activity would be useful in treating disorders associated with
10 cardiovascular disease. 25856 polypeptides of the present invention are useful in screening for modulators of 25856 activity.

Gene ID 32394

[0090] The human 32394 sequence (SEQ ID NO:55), known also as a voltage-gated potassium channel (KCNQ4), is approximately 2335 nucleotides long including
15 untranslated regions. The coding sequence, located at about nucleic acid 83 to 2170 of SEQ ID NO:55, encodes a 695 amino acid protein (SEQ ID NO:56).

[0091] As determined by TaqMan analysis, 32394 mRNA expression was upregulated in the fetal liver, megakaryocytes generated *in vitro*, the brain and in the heart.
20 32394 RNA was also expressed in the platelets from patients with coronary artery disease and in particular at higher levels in patients diagnosed with stable angina as compared with patients without coronary artery disease.

[0092] Although 32394 or KCNQ4 is found in sensory outer hair cells, and is mutated in dominant deafness [Cell 1999. 96(3):437-46], recent evidence indicates that at
25 least three genes are mutated in deafness. Therefore, affecting the function of 32394 or KCNQ4 as an anti-thrombotic would not have an effect on hearing. The KCNQ4 channels are also implicated in regulating the activity of excitable cells [Am J Physiol Cell Physiol. 2001. 280(4):C859-66]. Since ion fluxes are important regulators of platelet reactivity, the restricted expression in megakaryocytes plus the elevated RNA levels of
30 32394 in the platelets of patients with stable angina suggests that 32394 plays an important role in the progression from stable to unstable acute vascular lesion. Due to 32394 mRNA expression in the brain, liver and heart, along with its functional role, modulators of 32394 activity would be useful in treating disorders associated with cardiovascular disease,

including but not limited to thrombosis and atherosclerosis. 32394 polypeptides of the present invention are useful in screening for modulators of 32394 activity.

Gene ID 3484

5 [0093] The human 3484 sequence (SEQ ID NO:57), known also as a diacylglycerol kinase gamma (DGK γ), is approximately 3758 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 517 to 2892 of SEQ ID NO:57, encodes a 791 amino acid protein (SEQ ID NO:58).

[0094] As determined by TaqMan analysis, 3484 mRNA expression was
10 upregulated in the brain, megakaryocytes generated *in vitro* and heart. 3484 mRNA was also expressed at relatively high levels in platelets from patients with and without coronary artery disease and from normal volunteers.

[0095] Platelet adhesion to collagen results in platelet activation. Phosphatidic acid levels increase upon platelet adhesion to collagen [Analytical Biochemistry. 1990.
15 187(1):173-178]. Phosphatidic acid also amplifies the thrombotic response by increasing platelet chemotaxis and aggregation [Platelets. 2001. 12(3):163-170]. 3484 or DGK γ potentially plays a critical role in platelet activation and aggregation following platelet adhesion to collagen via the platelet collagen receptor. Due to 3484 mRNA expression in the brain and heart, along with its functional role, modulators of 3484 activity would be
20 useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 3484 polypeptides of the present invention are useful in screening for modulators of 3484 activity.

Gene ID 345

25 [0096] The human 345 sequence (SEQ ID NO:59), known also as a melanocortin-1 receptor (MC1-R), a GPCR, is approximately 1270 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 169 to 1122 of SEQ ID NO:59, encodes a 317 amino acid protein (SEQ ID NO:60).

[0097] As determined by TaqMan analysis, 345 mRNA expression was
30 upregulated the in heart, brain fetal liver, placenta, kidney, in umbilical cord blood, CD34+ cells and megakaryocytes generated *in vitro*. 345 RNA was also expressed in the platelets from patients with coronary artery disease and in normal volunteers.

[0098] The melanocortin-1 receptor or 345 is a Gs-linked receptor. Gs-linked receptors regulate adenylyl cyclase, which is an important mediator of platelet activation. The presence of MC1-R in megakaryocytes and platelets indicates that regulating the activity of 345 potentially controls platelet activation and thrombosis. Due to 345 mRNA expression in the heart, brain fetal liver, placenta, kidney, in umbilical cord blood, CD34+ cells and megakaryocytes, along with its functional role, modulators of 345 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 345 polypeptides of the present invention are useful in screening for modulators of 345 activity.

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Gene ID 9252

[0099] The human 9252 sequence (SEQ ID NO:61), known also as a hydroxymethyltransferase, is approximately 1599 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 13 to 1464 of SEQ ID NO:61, encodes a 483 amino acid protein (SEQ ID NO:62).

15

[00100] As determined by TaqMan analysis, 9252 mRNA was upregulated in the human liver when compared to normal liver tissues. Further analysis in a marmoset model showed 9252 regulation by cerivastatin in vivo.

[00101] Repression of 9252 reduces total cholesterol and triglycerides. 9252 gene expression regulates the hypolipidemic therapy cerivastatin. This regulation is identical to known genes involved in cholesterol biosynthesis (i.e. HMG CoA reductase). In addition, a known inhibitor of 9252 has lipid lowering effects in an in a rabbit vivo model. Due to 9252 mRNA expression in the liver, along with its functional role, modulators of 9252 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 9252 polypeptides of the present invention are useful in screening for modulators of 9252 activity.

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Gene ID 9135

[00102] The human 9135 sequence (SEQ ID NO:63), known also as a fatty aldehyde dehydrogenase, is approximately 1791 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 164 to 1621 of SEQ ID NO:63, encodes a 485 amino acid protein (SEQ ID NO:64).

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[00103] As determined by TaqMan analysis, 9135 mRNA was upregulated in the human liver when compared to normal liver tissues. Further analysis in a marmoset model showed 9135 regulation by cerivastatin in vivo.

[00104] Repression of fatty aldehyde dehydrogenase or 9135 potentially reduces total cholesterol and triglycerides. The fatty aldehyde dehydrogenase or 9135 gene is regulated by the hypolipidemic therapy cerivastatin. The regulation of 9135 is identical to known genes involved in cholesterol biosynthesis (i.e.HMG CoA reductase). In addition, fatty aldehyde dehydrogenase or 9135 is implicated in LTB4 degradation. LTB4 is a ligand for PPAR alpha. Inhibition of fatty aldehyde dehydrogenase or 9135 potentially results in increased levels of endogenous PPAR alpha ligand which is beneficial. Due to 9135 mRNA expression in the liver, along with its functional role, modulators of 9135 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 9135 polypeptides of the present invention are useful in screening for modulators of 9135 activity.

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Gene ID 10532

[00105] The human 10532 sequence (SEQ ID NO:65), known also as a serine aminotransferase, is approximately 1487 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 22 to 1200 of SEQ ID NO:65, encodes a 392 amino acid protein (SEQ ID NO:66).

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[00106] As determined by TaqMan analysis, 10532 mRNA was upregulated in the human liver when compared to normal liver tissues. Further analysis in a marmoset model showed 10532 regulation by cerivastatin/fenofibrate in vivo. In a human hepatocyte model, 10532 mRNA was also regulated by statin/PPAR alpha agonist in vitro. In addition, 10532 mRNA was also regulated by a high cholesterol diet in vivo.

25

[00107] Repression of serine aminotransferase or 10532 potentially reduces total cholesterol and triglycerides. 10532 gene expression is regulated by the hypolipidemic combination therapy cerivastatin/fenofibrate. 10532 is also regulated by high cholesterol diet. Regulation of 10532 is identical to known genes involved in cholesterol biosynthesis (i.e.HMG CoA reductase). Due to 10532 mRNA liver specific expression, along with its functional role, modulators of 10532 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 10532 polypeptides of the present invention are useful in screening for modulators of 10532 activity.

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Gene ID 18610

[00108] The human 18610 sequence (SEQ ID NO:67), known also as melanoma alpha kinase, is approximately 7280 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 214 to 5871 of SEQ ID NO:67, encodes a
5 1885 amino acid protein (SEQ ID NO:68).

[00109] As determined by TaqMan analysis, 18610 mRNA was upregulated in heart tissue. 18610, an alpha kinase, functions in the action of calcium mediated cellular responses. The increase in calcium mediated signaling process in vasculature causes
10 vasoconstriction. Therefore, the inhibition of alpha kinases or 18610 potentially results in lowering of calcium mediated signaling, thereby lowering blood pressure. Due to 18610 mRNA expression in the heart, along with its functional role, modulators of 18610 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 18610 polypeptides of the present invention are useful in
15 screening for modulators of 18610 activity.

Gene ID 8165

[00110] The human 8165 sequence (SEQ ID NO:69), known also as an aspartyl aminopeptidase, is approximately 1696 nucleotides long including untranslated regions.
20 The coding sequence, located at about nucleic acid 152 to 1579 of SEQ ID NO:69, encodes a 475 amino acid protein (SEQ ID NO:70).

[00111] As determined by TaqMan analysis, the 8165 mRNA was upregulated in the human liver when compared to normal liver tissues. Further analysis in a marmoset model showed 8165 regulation by cerivastatin in vivo. In a human hepatocyte model,
25 8165 was also regulated by statin/PPAR alpha agonist in vitro.

[00112] Repression of aspartyl aminopeptidase potentially reduces total cholesterol and triglycerides. 8165 expression is regulated by the hypolipidemic therapy cerivastatin in vivo (marmosets) and in vitro (human hepatocytes). The regulation of 8165 is identical to known genes involved in cholesterol biosynthesis (i.e.HMG CoA reductase. Due to 8165
30 mRNA expression in the liver, along with its functional role, modulators of 8165 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 8165 polypeptides of the present invention are useful in screening for modulators of 8165 activity.

Gene ID 2448

[00113] The human 2448 sequence (SEQ ID NO:71), known also as a lysosphingolipid receptor (EDG3), is approximately 2327 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1124 to 2260 of
5 SEQ ID NO:71, encodes a 378 amino acid protein (SEQ ID NO:72).

[00114] As determined by TaqMan analysis, 2448 mRNA was highly expressed in human arteries, kidneys and cultured coronary smooth muscle cells. Further TaqMan analysis showed that 2448 mRNA was expressed in cultured human umbilical vein endothelial cells (HUVECs) and in heart tissue. In addition, rat models of vascular tone
10 indicated that 2448 was upregulated in hypertensive rat aortas while downregulated in aortas of rats treated with antihypertensives.

[00115] 2448 or EDG3, is a lysosphingolipid receptor, with sphingosine 1-phosphate (S1P) as its ligand. S1P and 2448's involvement in vascular tone and atherosclerosis is through the signaling cascades that the 2448 receptor triggers. 2448 is
15 Gi, Gq and G12/13 coupled (Ann. Rev. Pharmacol. Toxicol., 2001, 41: 507-534) leading to the activation of Rho, Rac and MAPK signaling pathways while inhibiting the Adenylate cyclase pathway. The resulting intracellular Ca²⁺ mobilization (J Biochem, 2002, 362; 349-357) and kinase cascade activation plays a role in smooth muscle cell depolarization and the maintenance of vascular tone. Therefore, antagonizing 2448 blocks
20 the release of intracellular calcium and promotes hyperpolarization of the cell and vasorelaxation. Due to 2448 mRNA expression in the arteries, kidneys and cultured coronary smooth muscle cells brain, along with its functional role, modulators of 2448 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis and hypertension. 2448 polypeptides of the
25 present invention are useful in screening for modulators of 2448 activity.

Gene ID 2445

[00116] The human 2445 sequence (SEQ ID NO:73), known also as a lysophosphatidic acid receptor (EDG2), is approximately 1576 nucleotides long including
30 untranslated regions. The coding sequence, located at about nucleic acid 27 to 1121 of SEQ ID NO:73, encodes a 364 amino acid protein (SEQ ID NO:74).

[00117] As determined by TaqMan analysis, 2445 mRNA was highly expressed in human arteries, cultured coronary smooth muscle cells and central nervous system (CNS) structures, such as spinal cord (SC), cortex, hypothalamus and dorsal root ganglion (DRG).

Further TaqMan analysis indicated that 2445 mRNA was also present at lower levels in heart, kidney, skeletal muscle, adipose and various tissues of the immune system.

[00118] 2445 or EDG2, is a lysophosphatidic acid receptor, with LPA as its agonist.

2445 and its agonist, LPA, are involved in multiple intracellular signaling cascades,

5 including those involved in the maintenance of vascular tone and the development of atherosclerosis (Journal of Biological Chemistry, 2000, 275: 27520-27530). The high expression of 2445 in peripheral blood vessels indicates a role for 2445 in vascular function. 2445 is Gi/o, Gq/11/14 and G12/13 coupled (Ann. Rev. Pharmacol. Toxicol.,

2001, 41: 507-534). LPA stimulation leads to activation of the Ras-Raf-ERK pathway,

10 adenylate cyclase inhibition, phospholipase D activation and Ca²⁺ mobilization.

Stimulation of 2445 by LPA mobilizes intracellular Ca²⁺ via activation of phospholipase C (Molecular Pharmacology, 1998, 54: 881-888). Therefore, antagonizing 2445 blocks the release of intracellular calcium and activation of the ERK and Ras pathways and promotes hyperpolarization of the cell, leading to vasorelaxation. The receptor blockade also

15 protects against smooth muscle cell proliferation which is prevalent in atherosclerosis.

Due to 2445 mRNA expression in the arteries, cultured coronary smooth muscle cells, spinal cord, cortex, hypothalamus and dorsal root ganglion, along with its functional role, modulators of 2445 activity would be useful in treating disorders associated with

cardiovascular disease including but not limited to atherosclerosis and hypertension. 2445

20 polypeptides of the present invention are useful in screening for modulators of 2445 activity.

Gene ID 64624

25 [00119] The human 64624 sequence (SEQ ID NO:75), known also as a zinc transporter (ZIP4), is approximately 2192 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 101 to 2044 of SEQ ID NO:75, encodes a 647 amino acid protein (SEQ ID NO:76).

[00120] As determined by TaqMan analysis, 64624 mRNA was expressed at the
30 highest levels in kidney and brain. 64624 mRNA was also present at high levels in megakaryocytes generated in vitro. In addition, 64624 mRNA was present in the platelets of patients with coronary artery disease and from normal volunteers.

[00121] 64624 is a zinc transporter that has been implicated in dietary zinc uptake [AM J Hum Genet. 2002. 71(1):66-73]. Evidence suggests that zinc potentiates the

aggregation response via the protein kinase C pathway [J Lab Clin Med. 1994. 123(1):102-109]. Zinc is also an important cofactor for the interaction of platelets with the coagulation mechanism. For example, zinc released from platelets acts as a cofactor for histidine-rich glycoprotein binding to heparin, preventing heparin from interacting with anti-thrombin III and thereby promoting fibrin formation [JBC 1997.272(21):13541-47]. In addition, zinc is a cofactor of intrinsic coagulation activation. Therefore, regulation of the 64624 would provide a means to inhibit platelet-mediated thrombus formation. Due to 64624 mRNA expression in the kidney and brain, along with its functional role, modulators of 64624 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to thrombosis and atherosclerosis. 64624 polypeptides of the present invention are useful in screening for modulators of 64624 activity.

Gene ID 84237

[00122] The human 84237 sequence (SEQ ID NO:77), known also as a zinc transporter (hzntl1), is approximately 2952 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 202 to 2499 of SEQ ID NO:77, encodes a 765 amino acid protein (SEQ ID NO:78).

[00123] As determined by TaqMan analysis, 84237 mRNA was expressed at highest levels in megakaryocytes generated in vitro, in fetal liver and brain. 84237 mRNA was also present at high levels in the platelets of patients with coronary artery disease and from normal volunteers.

[00124] 84237 or hzntl1 is the human ortholog to a murine zinc transporter, mzntl1. Zinc is an important cofactor for the interaction of platelets with the coagulation mechanism. For example, zinc released from platelets acts as a cofactor for histidine-rich glycoprotein binding to heparin, preventing heparin from interacting with anti-thrombin III and thereby promoting fibrin formation [JBC 1997.272(21):13541-47]. Zinc is also a cofactor of intrinsic coagulation activation. Evidence indicates that zinc potentiates the aggregation response via the protein kinase C pathway [J Lab Clin Med. 1994. 123(1):102-109]. Therefore, regulation of the 84237, hzntl1, would provide a means to inhibit platelet-mediated thrombus formation. Due to 84237 mRNA expression in megakaryocytes generated in vitro and in fetal liver and brain, along with its functional role, modulators of 84237 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 84237

polypeptides of the present invention are useful in screening for modulators of 84237 activity.

Gene ID 8912

5 **[00125]** The human 8912 sequence (SEQ ID NO:79), known also as an alkyl-dihydroxyacetonephosphate synthase (alkyl-DHAP synthase), is approximately 2074 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 16 to 1992 of SEQ ID NO:79, encodes a 658 amino acid protein (SEQ ID NO:80).

10 **[00126]** As determined by TaqMan analysis, 8912 mRNA was expressed at the highest levels in brain, in fetal liver and in bone marrow progenitor cells expressing CD15. Further TaqMan experiments indicated that 8912 mRNA was present at high levels in megakaryocytes generated in vitro in kidney and in heart. 8912 mRNA was also present in the platelets from patients with and without coronary artery disease and from normal
15 volunteers.

[00127] 8912 or alkyl-dihydroxyacetonephosphate synthase (alkyl-DHAP synthase) is a peroxisomal enzyme essential for the biosynthesis of ether phospholipids. Deficiencies in DHAP-synthase affects a specific phospholipid, plasmalogen, reducing its content in the plasma membrane of cells [J.B.C. 1998. 273(17):10296-10301; P.N.A.S..
20 1997. 94:4475-4480]. Lipid abnormalities exist in patients with diabetes. The platelets of diabetic patients are considered to be more reactive with regard to aggregation and thrombosis. Evidence exists demonstrating that in rodent models of diabetes, plasmalogen levels are altered [Int J. Biochem. 1994. 26(6):759-767]. Altered levels of alkyl-DHAP synthase found in the platelets of diabetic patients with coronary artery disease is found to
25 contribute to the hyper-reactive phenotype associated with these diabetics' platelets. Due to 8912 mRNA expression in brain, in fetal liver and in bone marrow progenitor cells expressing CD15, along with its functional role, modulators of 8912 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 8912 polypeptides of the present invention are useful in
30 screening for modulators of 8912 activity.

Gene ID 2868

[00128] The human 2868 sequence (SEQ ID NO:81), known also as a T-cell death associated gene (TDAG8), is approximately 1753 nucleotides long including untranslated

regions. The coding sequence, located at about nucleic acid 523 to 1536 of SEQ ID NO:81, encodes a 337 amino acid protein (SEQ ID NO:82).

[00129] As determined by TaqMan analysis, 2868 mRNA was predominantly expressed in lymphoid tissues, such as the spleen and tonsil. Further TaqMan experiments showed that 2868 mRNA was also expressed in human arteries and diseased aortas and some central nervous system structures, such as the spinal cord and hypothalamus. In pooled samples of diseased versus normal human arteries, there was a two-fold upregulation of 2868 mRNA in atherosclerotic vessels. In a rat model of hypertension, there was a downregulation of 2868 mRNA in the aortas of animals treated with anti-hypertensives, compared to their vehicle-treated controls.

[00130] Stimulation of 2868 results in increases in intracellular calcium and in inhibition of cAMP. Blockade of the 2868 receptor would result in a decreased immune response during the process of atherosclerotic lesion formation and would slow the progression of atherosclerosis. Due to 2868 mRNA expression in the spleen, tonsils, arteries, spinal cord and hypothalamus, along with its functional role, modulators of 2868 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 2868 polypeptides of the present invention are useful in screening for modulators of 2868 activity.

Gene ID 283

[00131] The human 283 sequence (SEQ ID NO:83), known also as a galanin receptor type 1 (Gall-R), is approximately 1053 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1 to 1050 of SEQ ID NO:83, encodes a 349 amino acid protein (SEQ ID NO:84).

[00132] As determined by TaqMan analysis, 283 mRNA was highly expressed in the central nervous system (CNS), particularly the brain and spinal cord. Further Taqman analysis indicated that 283 mRNA was expressed in the human kidneys, arteries and veins. The 283 gene product was also detected in rat tissues and was down-regulated in kidneys of rats which were sensitive to salt-induced hypertension. Our data showed an enrichment of 283 over the other galanin receptors in the kidney.

[00133] Galanin stimulation of 283 or Gall-R causes a decrease in cAMP in the cell and the opening of inwardly rectifying K⁺ channels (TiPS, March 2000, 21: 109-117). The high expression of the 283 receptor in CNS structures suggests a central functional role. Our data, describing good expression in peripheral tissues, particularly the kidney and

vessels, suggest a novel role for this receptor in cardiovascular function. Therefore, antagonising the 283 receptor would prevent the influx of K⁺ and increase the intracellular levels in cAMP, promoting hyperpolarization of the cell and vasorelaxation. Due to 283 mRNA expression in the brain, spinal cord, kidney, arteries and veins, along with its functional role, modulators of 283 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to atherosclerosis. 283 polypeptides of the present invention are useful in screening for modulators of 283 activity.

Gene ID 2554

10 [00134] The human 2554 sequence (SEQ ID NO:85), known also as mGlu8 receptor, is approximately 3321 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 58 to 2784 of SEQ ID NO:85, encodes a 908 amino acid protein (SEQ ID NO:86).

[00135] As determined by TaqMan analysis, 2554 mRNA was expressed in the liver. Further Taqman analysis on specific rodent models of cardiovascular disease indicated that 2554 mRNA was upregulated in vitro in statin/PPAR (peroxisomal proliferators activated receptor) models. 2554 mRNA was also repressed by cholesterol in apolipoprotein (apo E) cholesterol models, but upregulated in cholethryramine models. 2554 plays a potential role in mediating the effects on hepatic TG. Therefore, inhibiting 2554 potentially has beneficial effects on lipid profiles.

[00136] As determined by TaqMan analysis, 2554 mRNA expression was upregulated in 5-fold in failing vs. normal human hearts. The human metabotropic Glutamate receptor type 8 (mGlu8) belongs to the superfamily of G-protein-coupled receptors (GPCRs). This receptor is a member of the group III metabotropic glutamate receptors, which also includes mGlu4, mGlu6 and mGlu7. Glutamate is a neurotransmitter commonly known to produce excitatory effects in the mammalian central nervous system. Scientific literature has also demonstrated that glutamate levels decrease in ischemic hearts. Since mGlu8 can affect intracellular levels of cAMP due to its coupling via G_i, upregulation of the expression of mGlu8 has direct effects on contractility of the heart. Thus, mGlu8 may potentially be implicated in cardiovascular diseases, such as ischemia and heart failure.

[00137] Due to 2554 mRNA expression in the liver and in failing human heart, along with its functional role, modulators of 2554 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to

atherosclerosis, dyslipidemia, ischemia and heart failure. 2554 polypeptides of the present invention are useful in screening for modulators of 2554 activity.

Gene ID 9464

- 5 [00138] The human 9464 sequence (SEQ ID NO:87), known also as an ATP dependent inward rectifying K channel, is approximately 2896 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 439 to 1578 of SEQ ID NO:87, encodes a 379 amino acid protein (SEQ ID NO:88).
- 10 [00139] As determined by TaqMan analysis, 9464 mRNA was expressed in the liver. Further Taqman analysis on specific rodent models of cardiovascular disease indicated that 9464 mRNA was repressed in apolipoprotein (apo E) cholesterol models. Published literature indicates that ligands for the 9464 receptor have beneficial lipid lowering effects in pre-clinical models. Therefore, antagonists and agonists of 9464 potentially have beneficial effects on lipid profiles. Due to 9464 mRNA expression in the
- 15 liver, along with its functional role, modulators of 9464 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to atherosclerosis and dyslipidemia. 9464 polypeptides of the present invention are useful in screening for modulators of 9464 activity.

20 **Gene ID 17799**

- [00140] The human 17799 sequence (SEQ ID NO:89), known also as a cytidyl transferase, is approximately 1856 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 67 to 1236 of SEQ ID NO:89, encodes a 389 amino acid protein (SEQ ID NO:90).
- 25 [00141] As determined by TaqMan analysis, indicated that 17799 mRNA was expressed in the human liver. Further TaqMan analysis on specific models of cardiovascular disease indicated that 17799 mRNA was repressed in apolipoprotein (apo E) cholesterol models and niacin marmoset models. Published literature indicates that the 17799 enzyme is linked to Phosphoethanolamine (PE) biosynthesis and increased PE
- 30 biosynthesis is associated with increased levels of TG transport from hepatocytes. PE is also pro-thrombotic and PE is a target for glycation, enhancing the atherosclerotic potential of LDL. Inhibition of 17799 potentially has beneficial effects on lipid profiles. Due to 17799 mRNA expression in the human liver, along with its functional role, modulators of 17799 activity would be useful in treating disorders associated with cardiovascular disease

including but not limited to atherosclerosis and dyslipidemia. 17799 polypeptides of the present invention are useful in screening for modulators of 17799 activity.

Gene ID 26686

5 [00142] The human 26686 sequence (SEQ ID NO:91), known also as acyl co A synthase, is approximately 3165 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 420 to 2582 of SEQ ID NO:91, encodes a 720 amino acid protein (SEQ ID NO:92).

[00143] As determined by TaqMan analysis, 26686 mRNA was expressed in the
10 liver. Further Taqman analysis on specific models of cardiovascular disease indicated that 26686 mRNA was upregulated in feno/ceriva marmoset and statin/PPAR (peroxisomal proliferators activated receptor) in vitro hep models, but 26686 mRNA showed a decreased expression leves in monkey cholesterol and apolipop protein (apo E) cholesterol models. Published literature indicates that 26686 plays a role of in lipid metabolism. Therefore,
15 inhibiting 26686 potentially leads to lower lipid levels. Due to 26686 mRNA expression in the liver, along with its functional role, modulators of 26686 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis and dyslipidemia. 26686 polypeptides of the present invention are useful in screening for modulators of 26686 activity.

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Gene ID 43848

[00144] The human 43848 sequence (SEQ ID NO:93), known also as N-acyltransferase, is approximately 1124 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 135 to 1025 of SEQ ID NO:93,
25 encodes a 296 amino acid protein (SEQ ID NO:94).

[00145] As determined by TaqMan analysis, 43848 mRNA was increased in cholestyramine and fenofibrate/cerivastatin marmoset models, but 43848 expression levels were decreased in apolipop protein (apo E) cholesterol model. Published literature indicates that 43848 is part of the FXR nuclear receptor negative feedback loop for bile
30 acid synthesis. Antagonist for FXR results in cholesterol reduction. Therefore, inhibiting 43848 has beneficial effects on lipid profiles. Due to 43848 mRNA expression in cholestyramine and fenofibrate/cerivastatin marmoset models, along with its functional role, modulators of 43848 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis and dyslipidemia.

43848 polypeptides of the present invention are useful in screening for modulators of 43848 activity.

Gene ID 32135

5 [00146] The human 32135 sequence (SEQ ID NO:95), known also as tetrahydrofolate dehydrogenase, is approximately 3040 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 111 to 2819 of SEQ ID NO:95, encodes a 902 amino acid protein (SEQ ID NO:96).

10 [00147] As determined by TaqMan analysis, 32135 mRNA was expressed in the human liver. Taqman analysis on specific models of cardiovascular disease indicated that 32135 mRNA was repressed in apolipoprotein (apo E) cholesterol, monkey cholesterol and niacin models. Published literature indicates that mutations in methylene tetrahydrofolate reductase associated with elevated homocysteine levels. 32135 plays a potential role in homocysteine biosynthesis. Therefore, inhibiting 32135 has beneficial effects on lipid profiles. Due to 32135 mRNA expression in the liver, along with its functional role, modulators of 32135 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis and dyslipidemia. 32135 polypeptides of the present invention are useful in screening for modulators of 32135 activity.

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Gene ID 12208

[00148] The human 12208 sequence (SEQ ID NO:97), known also as a human small conductance calcium-activated potassium channel protein 3 (KCNN3), is approximately 3095 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 334 to 2544 of SEQ ID NO:97, encodes a 736 amino acid protein (SEQ ID NO:98).

25 [00149] As determined by TaqMan analysis, 12208 mRNA was expressed in the spleen, kidney, heart and brain. Further TaqMan analysis indicated that 12208 was expressed at high levels in megakaryocytes generated *in vitro*. In addition, 12208 RNA is detected at high levels in the platelets of patients with coronary artery disease and in platelets from normal volunteers.

30 [00150] The calcium-activated potassium channel, KCNN3 or 12208 is activated by intracellular calcium. Calcium spikes are an essential component of platelet activation. Increased levels of KCNN3 or 12208 in the platelets of patients with stable angina,

indicates an increased platelet reactivity in these patients. Therefore, inhibition of KCNN3 or 12208, provides a means to inhibit platelet aggregation and thrombus formation. Due to 12208 mRNA expression in the spleen, kidney, heart and brain, along with its functional role, modulators of 12208 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to thrombosis and atherosclerosis. 12208 polypeptides of the present invention are useful in screening for modulators of 12208 activity.

Gene ID 2914

[00151] The human 2914 sequence (SEQ ID NO:99), known also as a mosaic serine protease, is approximately 2393 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 88 to 1833 of SEQ ID NO:99, encodes a 581 amino acid protein (SEQ ID NO:100).

[00152] As determined by TaqMan analysis, 2914 mRNA was expressed at the highest levels in megakaryocytes generated *in vitro* and in placenta. Further Taqman analysis indicated that 2914 RNA is detected in the platelets of patients with coronary artery disease

[00153] The mosaic serine protease or 2914 is spliced with and without a transmembrane domain [BBA 2001. 19;1518(1-2):204-409]. Serine proteases play an essential role in maintaining hemostasis and in promoting thrombogenesis. Therefore, inhibition of the mosaic serine protease, 2914, would provide a means to inhibit thrombus formation. Due to 2914 mRNA expression in megakaryocytes generated *in vitro* and in the placenta, along with its functional role, modulators of 2914 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 2914 polypeptides of the present invention are useful in screening for modulators of 2914 activity.

Gene ID 51130

[00154] The human 51130 sequence (SEQ ID NO:101), known also as an peptidylarginine deiminase (PAD), is approximately 2263 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 27 to 2018 of SEQ ID NO:101, encodes a 663 amino acid protein (SEQ ID NO:102).

[00155] As determined by TaqMan analysis, 51130 mRNA was expressed in hematopoietic cells and mononuclear cells and CD14 positive cells (monocytes). Further

TaqMan analysis indicated that 51130 mRNA was present at high levels in megakaryocytes generated *in vitro* and in the platelets of patients with coronary artery disease and from normal volunteers.

[00156] PAD (51130) is a peptidylarginine deiminase that is implicated in myeloid differentiation [JBC. 1999. 274(39):27786-27792]. Recent results indicate that PAD converts an essential arginine residue on antithrombin III (ATIII) to citrulline, thereby negatively affecting the function of this important anticoagulant. Deimination of antithrombin III results in an increased affinity of ATIII for heparin thus inactivating the thrombin-neutralizing function of ATIII [JBC 1997. 272(32): 19652-19655]. The inactivation of ATIII by platelet released PAD or 51130 would create an imbalance in hemostasis by accelerating thrombin activation of platelets and fibrin formation. Therefore, inhibition of the platelet peptidylarginine deiminase provides a means to inhibit platelet-mediated thrombus formation. Due to 51130 mRNA expression in hematopoietic cells and mononuclear cells, along with its functional role, modulators of 51130 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 51130 polypeptides of the present invention are useful in screening for modulators of 51130 activity.

Gene ID 19489

[00157] The human 19489 sequence (SEQ ID NO:103), known also as a novel secreted phospholipase A2 (sPLA2), is approximately 1204 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 143 to 712 of SEQ ID NO:103, encodes a 189 amino acid protein (SEQ ID NO:104).

[00158] As determined by TaqMan analysis, 19489 mRNA was expressed in megakaryocytes generated *in vitro*, in erythroid cells and in heart. In addition, 19489 RNA was present at very high levels in the platelets of patients with coronary artery disease and from normal volunteers

[00159] sPLA2 or 19489 is a novel secreted phospholipase A2 with as of yet an undefined function [JBC. 2000. 275(51):39823-39826]. Lysophosphatidic acid is a lipid mediator and platelet agonist. Lysophosphatidic acid also binds and activates endothelial cells. Lysophosphatidic acid is generated by the enzymatic activity of phospholipases. The high levels of sPLA2 or 19489 in platelets and its restricted expression indicate that sPLA2 or 19489 is an important enzyme during acute coronary syndrome. sPLA2 or 19489 is potentially responsible for the generation of lysophosphatidic acid and its increased plasma

levels following acute coronary events. Therefore, inhibition of the platelet sPLA2 or 19489, would inhibit platelet-endothelial cell interactions and thrombus formation. Due to 19489 mRNA expression in megakaryocytes generated *in vitro*, in erythroid cells and in heart, along with its functional role, modulators of 19489 activity would be useful in
5 treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 19489 polypeptides of the present invention are useful in screening for modulators of 19489 activity.

Gene ID 21833

10 [00160] The human 21833 sequence (SEQ ID NO:105), known also as the enzyme kynureninase, is approximately 1637 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 107 to 1504 of SEQ ID NO:105, encodes a 465 amino acid protein (SEQ ID NO:106).

[00161] As determined by TaqMan analysis, 21833 mRNA was expressed at highest
15 levels in the human liver, in macrophages and tonsil. Further TaqMan analysis indicated that 21833 mRNA was upregulated in diseased human arteries when compared to normal vessels. In cultured human monocytes and macrophages, 21833 was upregulated after interferon gamma and CD40-ligand stimulation. By laser capture microdissection and TM analysis, 21833 was enriched in the macrophage and monocyte-rich lesion area of
20 atherosclerotic arteries.

[00162] 21833 or kynureninase is a downstream enzyme involved in tryptophan metabolism (Saito et al., AJP-Renal Physiology, 279: 3, F565-F572, 2000). Kynureninase converts kynurenine to anthranilic acid and 3-hydroxykynurenine to 3-hydroxyanthranilic acid. The downstream product of 3-hydroxyanthranilic acid metabolism is quinolinic acid
25 formation. Quinolinic acid is an agonist of the NMDA-receptor and is excitotoxic to neural cells; it has been found in macrophages stimulated by interferon gamma and TNFalpha (Chiarugi, A et al., Journal of Neuroimmunology, 120: 1-2, 190-198.) Therefore, inhibiting 21833 or kynureninase leads to the reduction of the toxin, quinolinic acid, which can reduce atherosclerotic injury in vessels. Due to 21833 mRNA expression
30 in the human liver, in macrophages and tonsil, along with its functional role, modulators of 21833 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to thrombosis and atherosclerosis. 21833 polypeptides of the present invention are useful in screening for modulators of 21833 activity.

Gene ID 2917

[00163] The human 2917 sequence (SEQ ID NO:107), known also as serine protease 23, is approximately 1647 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 105 to 1256 of SEQ ID NO:107, encodes a
5 383 amino acid protein (SEQ ID NO:108).

[00164] As determined by TaqMan analysis, 2917 mRNA was expressed at highest levels in human arteries, veins, HUVECs, smooth muscle cells and vascular rich organs. By transcriptional profiling, there was upregulation of 2917 mRNA in response to anti-hypertensive therapy in normotensive rat aortas. By angiotensin1 receptor blockade, L-type calcium channel blockade and by ATP-dependent potassium channel opening
10 indicated that 2917 mRNA was upregulated.

[00165] Serine protease 23 or 2917 is a novel serine protease cloned from human umbilical vein endothelial cells. Its abundance in vascularized tissues such as the aorta, vein, heart and kidney; its presence in endothelial cells and smooth muscle cells; and its
15 regulation in a rat model of vascular tone gene discovery, implicate 2917 in the maintenance of systemic blood pressure. Therefore, antagonists of 2917 would function in the reduction of peripheral vascular resistance and decrease blood pressure. Due to 2917 mRNA expression in the arteries, veins, HUVECs, smooth muscle cells and vascular rich organs, along with its functional role, modulators of 2917 activity would be useful in
20 treating disorders associated with cardiovascular disease, including but not limited to thrombosis and atherosclerosis. 2917 polypeptides of the present invention are useful in screening for modulators of 2917 activity.

Gene ID 59590

[00166] The human 59590 sequence (SEQ ID NO:109), known also as heart alpha-kinase (HAK), is approximately 5375 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 199 to 4794 of SEQ ID NO:109, encodes a 1531 amino acid protein (SEQ ID NO:110).
25

[00167] As determined by TaqMan analysis, 59590 mRNA was upregulated in the experiments comparing human heart left ventricle samples of 12 congestive heart failure patients (CHF) with 7 non-failing patients (NF, control). 59590 mRNA expression was restricted to heart and skeletal muscle and was expressed to a lesser degree in kidney, osteoblasts and smooth muscle cells.
30

[00168] Heart alpha-kinase (HAK) or 59590 belongs to a new family of kinases (alpha-kinases) that is unlike the conventional serine/threonine/tyrosine kinases. Family members include eukaryotic elongation factor-2 kinase (eEF-2K) and *Dictyostelium*'s myosin heavy chain kinase A, B and C (MHCK A, B and C). HAK or 59590 is highly expressed in heart and skeletal muscle and is regulated in heart failure. Because HAK or 59590 belongs to the same class as *Dictyostelium*'s MHCK A, HAK or 59590 potentially plays a role in sarcomere assembly and in contraction efficiency which is known to be impaired in heart failure patients. Muscle contracts when cytosolic calcium is increased (released from sarcoplasmic reticulum at every cycle) through actomyosin interactions that forms part of the sarcomere. During the progression of heart failure, the myocytes try to compensate for an increase workload by increasing in size (hypertrophy). At the late stage of heart failure, there is loss of contractile elements, marked disruption of Z bands and a severe disruption of the normal parallel arrangement of sarcomere resulting in impaired contraction. The upregulation of HAK or 59590 in heart failure potentially causes the impaired contraction. Therefore inhibitors to HAK or 59590 are beneficial in the treatment of heart failure and other cardiovascular disorders. Due to 59590 mRNA expression in the heart and skeletal muscle, along with its functional role, modulators of 59590 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to ischemia and heart failure. 59590 polypeptides of the present invention are useful in screening for modulators of 59590 activity.

Gene ID 15992

[00169] The human 15992 sequence (SEQ ID NO:111), known also as cardiolipin synthase, is approximately 1241 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 94 to 999 of SEQ ID NO:111, encodes a 301 amino acid protein (SEQ ID NO:112).

[00170] As determined by TaqMan analysis, 15992 mRNA showed a 5 fold upregulation in ischemic versus normal heart samples in ischemic heart samples. Further Taqman analysis indicated that 15992 mRNA expression was restricted with the highest level in CHF heart followed by lower levels of expression in colon tumor, prostate tumor and normal adrenal gland.

[00171] Cardiolipin synthase is a member of this family of transferases and cardiolipin, associated primarily with the inner mitochondrial membrane of mammalian cells, comprises approximately 15% of the entire cardiac glycerolphospholipid mass.

Cardiolipin is required for a number of mitochondrial enzymes involved in energy metabolism; content of cardiolipin is important for activation of these enzymes. Ischemic events will decrease the cardiolipin content as well as the level of phosphorylation through cytochrome oxidase. Cardiolipin is enriched in oxidatively sensitive acyl residues, addition of cardiolipin but not peroxidized cardiolipin will almost completely restore activity of cytochrome oxidase. Therefore, the upregulation of 15992 potentially results in either synthesis of an alternate phospholipid that replaces cardiolipin in the mitochondrial membrane or alters its molecular composition resulting in a decrease in cytochrome oxidase activity. Due to 15992 mRNA expression in the brain and heart, along with its functional role, modulators of 15992 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to ischemia and heart failure. 15992 polypeptides of the present invention are useful in screening for modulators of 15992 activity.

Gene ID 2094

[00172] The human 2094 sequence (SEQ ID NO:113), known also as human germinal center kinase (GCK), which is approximately 2906 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 40 to 2499 of SEQ ID NO:113, encodes a 765 amino acid protein (SEQ ID NO:114).

[00173] As determined by TaqMan analysis, 2094 mRNA was expressed at highest levels in brain and in megakaryocytes generated *in vitro*. 2094 mRNA was also present in the placenta. Further TaqMan analysis indicated that 2094 mRNA was detected in the platelets of apheresed normal donors and in the platelets of patients with coronary artery disease and in platelets from normal volunteers. 2094 mRNA was also present at statistically significant elevated levels in the platelets of patients with angina as compared with patients with no coronary artery disease or normal volunteers.

[00174] The germinal center kinase, GCK or 2094, activates at least two MAP kinases, MEKK1 and MLK3 [MCB. 2002. 22(3):737-749]. MLK3 activates MKK4 through a phosphorylation event, and MKK4 activates JNK kinase also by phosphorylation [JBC.2000. 275(36);27893-27900]. JNK activation is required for platelet aggregation. GCK or 2094 also activates MEKK1 inducing autophosphorylation of MEKK1 however, evidence exists indicating that MEKK1 is not a mediator of platelet aggregation [JBC. 2002. Sep 23 9epub ahead of print]. The high levels of 2094 mRNA found in platelets and the elevated levels found in the platelets of patients with angina indicates that 2094

regulates JNK-mediated platelet aggregation. Therefore, inhibiting 2094 provides a means to inhibit platelet-rich thrombus formation. Due to 2094 mRNA expression in the brain and in megakaryocytes, along with its functional role, modulators of activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to thrombosis and atherosclerosis. 2094 polypeptides of the present invention are useful in screening for modulators of 2094 activity.

Gene ID 2252

[00175] The human 2252 sequence (SEQ ID NO:115), known also as a human germinal center kinase III (MASK), is approximately 3335 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 221 to 1471 of SEQ ID NO:115, encodes a 416 amino acid protein (SEQ ID NO:116).

[00176] As determined by TaqMan analysis, 2252 mRNA was expressed in placenta and peripheral blood mononuclear cells. 2252 mRNA was expressed at high levels in megakaryocytes generated *in vitro*. In addition, 2252 mRNA is detected in the platelets of apheresed normal donors and at high levels in the platelets of patients with coronary artery disease and in platelets from normal volunteers.

[00177] 2252 is also known as germinal center kinase III subfamily member known as MASK. MASK or 2252 activity has been implicated in apoptosis [JBC. 2002. 277(8):5929-5939]. Recent reports compare the mechanisms driving platelet activation and degranulation to the apoptotic pathway [Blood.1999. 93(12):4222-4231]. Based on the literature and expression data, 2252 or MASK is a required signaling component regulating platelet activation and degranulation. Therefore, inhibition of 2252 or MASK, would inhibit platelet aggregation and thrombus formation. Due to 2252 mRNA expression in placenta, peripheral blood mononuclear cells and megakaryocytes generated *in vitro*, along with its functional role, modulators of 2252 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 2252 polypeptides of the present invention are useful in screening for modulators of 2252 activity.

Gene ID 3474

[00178] The human 3474 sequence (SEQ ID NO:117), known also as vesicular neurotransmitter transporter (VMAT2), is approximately 1800 nucleotides long including

untranslated regions. The coding sequence, located at about nucleic acid 114 to 1658 of SEQ ID NO:117, encodes a 514 amino acid protein (SEQ ID NO:118).

[00179] As determined by TaqMan analysis, 3474 mRNA was predominantly expressed in megakaryocytes, CD34+ progenitor cells and platelets. Further Taqman analysis also detected 3474 mRNA in normal human ovary.

[00180] The vesicular neurotransmitter transporter, VMAT2 or 3474, is known to sequester monoamines within synaptic vesicles. VMAT2 or 3474's expression in platelets indicate a similar function of sequestering monoamines within platelet granules. Platelet granule content is released upon platelet aggregation and is essential to the development of a thrombus. Our data indicates that this function is regulated in the platelets of patients with acute coronary syndromes, myocardial infarction and unstable angina as compared with patients with stable angina. Therefore, regulating 3474 or VMAT2 protects against the development of acute coronary syndromes. Due to 3474 mRNA expression in megakaryocytes, CD34+ progenitor cells and platelets, along with its functional role, modulators of 3474 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 3474 polypeptides of the present invention are useful in screening for modulators of 3474 activity.

Gene ID 9792

[00181] The human 9792 sequence (SEQ ID NO:119), known also as human high-affinity cationic amino acid transporter-1 (CAT-1), is approximately 2157 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 148 to 2037 of SEQ ID NO:119, encodes a 629 amino acid protein (SEQ ID NO:120).

[00182] As determined by TaqMan analysis, 9792 mRNA was expressed at highest levels in red blood cells and in megakaryocytes generated *in vitro*. Further TaqMan analysis indicated that 9792 mRNA was present in placenta and brain. In addition, 9792 mRNA was present in the platelets of patients with angina and in platelets from normal volunteers.

[00183] 9792 or CAT-1 is a cationic amino acid transporter involved in the transport of arginine, a precursor to the vasoamine, nitric oxide. Ischemia-reperfusion injury is a serious complication resulting from current treatments for clot resolution in the acute coronary syndromes. While endogenous production of nitric oxide is important for vascular tone, recent evidence suggests controlling the concentration of nitric oxide is

essential to preventing vascular injury and arrhythmias [J AM Coll Crdiol. 2001.38(2):546-554]. Regulation of CAT-1 on platelets provides a means to control nitric oxide production and the associated free radical injury following ischemia-reperfusion that occurs during thrombus formation and resolution. Therefore, inhibition of CAT-1 or 9792 protects against secondary coronary events. Due to 9792 mRNA expression in red blood cells and megakaryocytes generated *in vitro*, along with its functional role, modulators of 9792 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 9792 polypeptides of the present invention are useful in screening for modulators of 9792 activity.

Gene ID 15400

[00184] The human 15400 sequence (SEQ ID NO:121), known also as a human germinal center kinase called Traf2 and NCK interacting kinase (TNIK), is approximately 3807 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 1 to 3807 of SEQ ID NO:121, encodes a 1268 amino acid protein (SEQ ID NO:122).

[00185] As determined by TaqMan analysis, 15400 mRNA was expressed in brain and megakaryocytes generated *in vitro*. 15400 mRNA was detected in the platelets of apheresed normal donors and at high levels in the platelets of patients with coronary artery disease and in platelets from normal volunteers.

[00186] The germinal center kinase, 15400 or TNIK, activates the JNK signaling pathway [JBC. 1999. 273(43):30729-30737]. *In vitro* derived evidence suggests that exposure of platelets to VWF or thrombin activates JNK [Br J Haematol. 2000.109(4):851-856]. 15400 or TNIK is also implicated in actin based cytoskeletal reorganization. 15400 or TNIK phosphorylates gelsolin, the F-actin severing protein, in TNIK transfected cells [JBC. 1999. 273(43):30729-30737]. Shape change is an early step in platelet activation and requires gelsolin activity for actin reorganization [J Cell Biol. 1996.134(2):389-399]. Based on the literature and expression data, 15400 or TNIK plays an early step in platelet activation. Therefore, inhibition of TNIK, 15400, provides a means to inhibit platelet activation and thrombus formation. Due to 15400 mRNA expression in brain and megakaryocytes generated *in vitro*, along with its functional role, modulators of 15400 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to thrombosis and atherosclerosis. 15400 polypeptides of the present invention are useful in screening for modulators of 15400 activity.

Gene ID 1452

[00187] The human 1452 sequence (SEQ ID NO:123), known also as fgr kinase, is approximately 2354 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 20 to 2218 of SEQ ID NO:123, encodes a 529 amino acid protein (SEQ ID NO:124).

[00188] As determined by TaqMan analysis, 1452 mRNA was expressed in a variety of human tissues, including heart, spleen, pancreas, lung and tonsil. Further TaqMan analysis indicated that 1452 mRNA was expressed in macrophages, neutrophils, and erythroid progenitor cells. 1452 mRNA was also expressed in normal and atherosclerotic human arteries. In ApoE knockout mouse aortas, there was a substantial increase in expression of 1452 mRNA expression in the aortic arches compared to abdominal aortas; this expression was highly correlated with CD68 levels, indicating that 1452 mRNA was enriched in the macrophage rich lesion compartment of the vessel. In addition, 1452 mRNA was robustly expressed in cultured human monocytes and macrophages.

[00189] 1452 is a member of the src family of tyrosine kinases and is also called fgr kinase (Notario et al., J Cell Biol, 1989, 109: 3129-3136). It is thought that 1452 activity is partly responsible for macrophage migration and spreading. Given that macrophage recruitment and infiltration are a major aspect of the disease process in vessel wall atherosclerosis, inhibiting 1452 would result in a reduction of macrophage and eventually foam cell content in an atherosclerotic plaque and a diminished lesion size. Due to 1452 mRNA expression in the heart, spleen, pancreas, lung, tonsil, macrophages, neutrophils, and erythroid progenitor cells, along with its functional role, modulators of 1452 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to atherosclerosis. 1452 polypeptides of the present invention are useful in screening for modulators of 1452 activity.

Gene ID 6585

[00190] The human 6585 sequence (SEQ ID NO:125), known also as acyl peptide hydrolase, is approximately 2374 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 20 to 2218 of SEQ ID NO:125 encodes a 732 amino acid protein (SEQ ID NO:126).

[00191] As determined by TaqMan analysis, 6585 mRNA was highly expressed in human arteries, umbilical vein endothelial cells, coronary smooth muscle cells, congestive heart failure samples, kidneys, skeletal muscle and brain cortex. There was significant (t-test, $p=0.01$) upregulation demonstrated across human heart failure samples compared to non-failing ventricles. In rats, 6585 mRNA was moderately expressed in aortas. In 15 week old spontaneously hypertensive-stroke prone rats, there was trend toward upregulation of 6585 mRNA compared to Wistar Kyoto normotensive controls (not significant, $p=0.0527$).

[00192] 6585 is known as acyl peptide hydrolase, a member of a group of serine peptidases from the prolyl oligopeptidase family. Prolyl oligopeptidase is involved in blood pressure control and amnesia (Polgar L., The prolyl oligopeptidase family. Cell Mol Life Sci 2002 Feb;59(2):349-62). The enriched expression of the 6585 gene product in human vessels and the upregulation of 6585 in human failing myocardium as well as hypertensive rat aortas, indicates that 6585 plays multiple roles in the cardiovascular system. Specifically, antagonism of 6585 should reduce vascular tone and potentially reduce the progression of damage in congestive heart failure. Due to 6585 mRNA expression in human arteries, umbilical vein endothelial cells, coronary smooth muscle cells, hearts in congestive heart failure, kidneys, skeletal muscle and brain cortex, along with its functional role, modulators of 6585 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to ischemia and heart failure. 6585 polypeptides of the present invention are useful in screening for modulators of 6585 activity.

[00193] Various aspects of the invention are described in further detail in the following subsections:

Screening Assays:

[00194] The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules (organic or inorganic) or other drugs) which bind to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130,

19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

proteins, have a stimulatory or inhibitory effect on, for example, 1682, 6169, 6193, 7771,

14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371,

7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345,

5 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or 1682, 6169, 6193, 7771,

14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371,

7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345,

10 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, or have a stimulatory or inhibitory

effect on, for example, the expression or activity of a 1682, 6169, 6193, 7771, 14395,

29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077,

15 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252,

9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate. Compounds identified using the

assays described herein may be useful for treating cardiovascular diseases, *e.g.*,

20 atherosclerosis and/or thrombosis.

[00195] These assays are designed to identify compounds that bind to a 1682, 6169,

6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151,

60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856,

32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912,

25 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833,

2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, bind to other

intracellular or extracellular proteins that interact with a 1682, 6169, 6193, 7771, 14395,

29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077,

33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252,

30 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, and interfere with the interaction of

the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402,

7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848,

1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein with other intercellular or extracellular proteins. For example, in the case of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, which is a transmembrane receptor-type protein, such techniques can identify ligands for such a receptor. A 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein ligand or substrate can, for example, be used to ameliorate cardiovascular diseases, *e.g.*, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, thrombosis and endothelial cell disorders. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic compounds. Such compounds may also include other cellular proteins.

[00196] Compounds identified via assays such as those described herein may be useful, for example, for ameliorating cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis. In instances whereby a cardiovascular disease condition results from an overall lower level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression and/or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein in a cell or tissue, compounds that interact with the

1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein may include compounds which accentuate or amplify the activity of the bound 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Such compounds would bring about an effective increase in the level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein activity, thus ameliorating symptoms.

[00197] In other instances, mutations within the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene may cause aberrant types or excessive amounts of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins to be made which have a deleterious effect that leads to a cardiovascular disease. Similarly, physiological conditions may cause an excessive increase in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554,

9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression leading to a cardiovascular disease. In such cases, compounds that bind to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein may be identified that inhibit the activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Assays for testing the effectiveness of compounds identified by techniques such as those described in this section are discussed herein.

[00198] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The

biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

[00199] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

[00200] Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

[00201] In one embodiment, an assay is a cell-based assay in which a cell which expresses a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is determined. Determining the ability of the test compound to modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400,

1452 or 6585 activity can be accomplished by monitoring, for example, intracellular calcium, IP₃, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with angiogenesis, or the activity of a

5 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -regulated

10 transcription factor. The cell can be of mammalian origin, *e.g.*, an endothelial cell. In one embodiment, compounds that interact with a receptor domain can be screened for their ability to function as ligands, *i.e.*, to bind to the receptor and modulate a signal transduction pathway. Identification of ligands, and measuring the activity of the ligand-receptor complex, leads to the identification of modulators (*e.g.*, antagonists) of this

15 interaction. Such modulators may be useful in the treatment of cardiovascular disease.

[00202] The ability of the test compound to modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

20 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 binding to a substrate or to bind to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912,

25 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can also be determined. Determining the ability of the test compound to modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484,

30 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 binding to a substrate can be accomplished, for example, by coupling the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419,

18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate with a radioisotope or enzymatic label such that

5 binding of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

10 6585 substrate to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

15 6585 can be determined by detecting the labeled 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,

20 2252, 3474, 9792, 15400, 1452 or 6585 substrate in a complex. 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

25 2094, 2252, 3474, 9792, 15400, 1452 or 6585 could also be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554,

30 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 binding to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554,

9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate in a complex.

Determining the ability of the test compound to bind 1682, 6169, 6193, 7771, 14395,

29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077,

33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252,

9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be accomplished, for example, by

coupling the compound with a radioisotope or enzymatic label such that binding of the

compound to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427,

2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245,

58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445,

64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914,

51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

can be determined by detecting the labeled 1682, 6169, 6193, 7771, 14395, 29002, 33216,

43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419,

18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532,

18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686,

43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474,

9792, 15400, 1452 or 6585 compound in a complex. For example, compounds (*e.g.*,

1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747,

1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870,

25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,

8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489,

21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ligands or

substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the

radioisotope detected by direct counting of radioemmission or by scintillation counting.

Compounds can further be enzymatically labeled with, for example, horseradish

peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by

determination of conversion of an appropriate substrate to product.

[00203] It is also within the scope of this invention to determine the ability of a compound (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650,

14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ligand or substrate) to interact with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 without the labeling of either the compound or the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 (McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 .

[00204] In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610,

8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate) with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule. Determining the ability of the test compound to modulate the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule can be accomplished, for example, by determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to bind to or interact with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule.

[00205] Determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135,

10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or a biologically active fragment thereof, to bind to or interact with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to bind to or interact with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+} , diacylglycerol, IP_3 , cAMP), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response (*e.g.*, gene expression).

[00206] In yet another embodiment, an assay of the present invention is a cell-free assay in which a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

6585 protein or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to bind to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof is determined. Preferred biologically active portions of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins to be used in assays of the present invention include fragments which participate in interactions with non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecules, *e.g.*, fragments with high surface probability scores. Binding of the test compound to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof with a known compound which binds 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856,

32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, wherein determining the ability of the test compound to interact with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein comprises determining the ability of the test compound to preferentially bind to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 or biologically active portion thereof as compared to the known compound. Compounds that modulate the interaction of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 with a known target protein may be useful in regulating the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, especially a mutant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656,

32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 5 6585 protein.

[00207] In another embodiment, the assay is a cell-free assay in which a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 10 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 15 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate 20 the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 25 6585 protein can be accomplished, for example, by determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to bind to a 30 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489,

21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule by one of the methods described above for determining direct binding. Determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to bind to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[00208] In another embodiment, determining the ability of the test compound to modulate the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be accomplished by determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to further modulate the activity of a downstream effector of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135,

10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

[00209] In yet another embodiment, the cell-free assay involves contacting a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or biologically active portion thereof with a known compound which binds the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, wherein determining the ability of the test compound to interact with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein comprises determining the ability of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474,

9792, 15400, 1452 or 6585 protein to preferentially bind to or modulate the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule.

[00210] In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, or interaction of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then
5 combined with the test compound or the test compound and either the non-adsorbed target protein or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914,
10 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described
15 above. Alternatively, the complexes can be dissociated from the matrix, and the level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489,
20 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 binding or activity determined using standard techniques.

[00211] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371,
25 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252,
30 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated 1682, 6169, 6193, 7771,

14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or target molecules but which do not interfere with binding of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 1682, 6169, 6193, 7771, 14395, 29002,

33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,

5 2252, 3474, 9792, 15400, 1452 or 6585 protein or target molecule.

[00212] In another embodiment, modulators of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression are identified in a method

wherein a cell is contacted with a candidate compound and the expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856,

15 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein in the cell is determined. The level of expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein in the presence of the candidate compound is compared to the level of expression of 1682, 6169, 6193, 7771, 14395,

25 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein in the absence of the

30 candidate compound. The candidate compound can then be identified as a modulator of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489,

21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression based on this comparison. For example, when expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein expression. Alternatively, when expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein expression. The level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein expression in the cells can be determined by methods described herein for detecting 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419,

18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or protein.

5 [00213] In yet another aspect of the invention, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 10 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with 1682, 6169, 15 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ("1682, 6169, 6193, 20 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -binding proteins" or "1682, 6169, 25 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -bp") and are involved 30 in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

activity. Such 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -binding proteins are also likely to be involved in the propagation of signals by the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 targets as, for example, downstream elements of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -mediated signaling pathway. Alternatively, such 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -binding proteins are likely to be 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 inhibitors.

[00214] The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the

assay utilizes two different DNA constructs. In one construct, the gene that codes for a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein.

[00215] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be

confirmed *in vivo*, *e.g.*, in an animal such as an animal model for cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis, as described herein.

[00216] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulating agent, an antisense 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecule, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -specific antibody, or a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[00217] Any of the compounds, including but not limited to compounds such as those identified in the foregoing assay systems, may be tested for the ability to treat cardiovascular disease symptoms. Cell-based and animal model-based assays for the

identification of compounds exhibiting such an ability to ameliorate cardiovascular disease systems are described herein.

[00218] In one aspect, cell-based systems, as described herein, may be used to identify compounds which may act to treat at least one cardiovascular disease symptom.

5 For example, such cell systems may be exposed to a compound, suspected of exhibiting an ability to treat cardiovascular disease symptoms, at a sufficient concentration and for a time sufficient to elicit such an amelioration of cardiovascular disease symptoms in the exposed cells. After exposure, the cells are examined to determine whether one or more of the cardiovascular disease cellular phenotypes has been altered to resemble a more normal
10 or more wild type, non-cardiovascular disease phenotype. Cellular phenotypes that are associated with cardiovascular disease states include aberrant proliferation and migration, angiogenesis, deposition of extracellular matrix components, accumulation of intracellular lipids, and expression of growth factors, cytokines, and other inflammatory mediators.

[00219] In addition, animal-based cardiovascular disease systems, such as those
15 described herein, may be used to identify compounds capable of ameliorating cardiovascular disease symptoms. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies, and interventions which may be effective in treating cardiovascular disease. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to ameliorate cardiovascular disease
20 symptoms, at a sufficient concentration and for a time sufficient to elicit such an amelioration of cardiovascular disease symptoms in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of disorders associated with cardiovascular disease, for example, by counting the number of atherosclerotic plaques and/or measuring their size before and after treatment.

25 [00220] With regard to intervention, any treatments which reverse any aspect of cardiovascular disease symptoms should be considered as candidates for human cardiovascular disease therapeutic intervention. Dosages of test agents may be determined by deriving dose-response curves.

[00221] Additionally, gene expression patterns may be utilized to assess the ability
30 of a compound to ameliorate cardiovascular disease symptoms. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions.

Such conditions may include, but are not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, and arterial inflammation, including any of the control or experimental conditions described herein, for example, atherogenic cytokine stimulation of macrophages. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR. In one embodiment, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences may be used as probes and/or PCR primers for the generation and corroboration of such gene expression profiles.

[00222] Gene expression profiles may be characterized for known states, either cardiovascular disease or normal, within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

[00223] For example, administration of a compound may cause the gene expression profile of a cardiovascular disease model system to more closely resemble the control system. Administration of a compound may, alternatively, cause the gene expression profile of a control system to begin to mimic a cardiovascular disease state. Such a compound may, for example, be used in further characterizing the compound of interest, or may be used in the generation of additional animal models.

25 Cell- and Animal-Based Model Systems

[00224] Described herein are cell- and animal-based systems which act as models for cardiovascular disease. These systems may be used in a variety of applications. For example, the cell- and animal-based model systems may be used to further characterize differentially expressed genes associated with cardiovascular disease, *e.g.*, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . In addition, animal-

and cell-based assays may be used as part of screening strategies designed to identify compounds which are capable of ameliorating cardiovascular disease symptoms, as described, below. Thus, the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions which may be effective in treating cardiovascular disease. Furthermore, such animal models may be used to determine the LD50 and the ED50 in animal subjects, and such data can be used to determine the *in vivo* efficacy of potential cardiovascular disease treatments.

Animal-Based Systems

[00225] Animal-based model systems of cardiovascular disease may include, but are not limited to, non-recombinant and engineered transgenic animals.

[00226] Non-recombinant animal models for cardiovascular disease may include, for example, genetic models. Such genetic cardiovascular disease models may include, for example, ApoB or ApoR deficient pigs (Rapacz, *et al.*, 1986, *Science* 234:1573-1577) and Watanabe heritable hyperlipidemic (WHHL) rabbits (Kita *et al.*, 1987, *Proc. Natl. Acad. Sci USA* 84: 5928-5931). Transgenic mouse models in cardiovascular disease and angiogenesis are reviewed in Carmeliet, P. and Collen, D. (2000) *J. Pathol.* 190:387-405.

[00227] Non-recombinant, non-genetic animal models of atherosclerosis may include, for example, pig, rabbit, or rat models in which the animal has been exposed to either chemical wounding through dietary supplementation of LDL, or mechanical wounding through balloon catheter angioplasty. Animal models of cardiovascular disease also include rat myocardial infarction models (described in, for example, Schwarz, ER *et al.* (2000) *J. Am. Coll. Cardiol.* 35:1323-1330) and models of chronic cardiac ischemia in rabbits (described in, for example, Operschall, C *et al.* (2000) *J. Appl. Physiol.* 88:1438-1445).

[00228] Additionally, animal models exhibiting cardiovascular disease symptoms may be engineered by using, for example, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences described above, in conjunction with techniques for producing transgenic animals that are well known to those of skill in the art. For example, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427,

2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

5 gene sequences may be introduced into, and overexpressed in, the genome of the animal of interest, or, if endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 10 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences are present, they may either be overexpressed or, alternatively, be disrupted in order to underexpress or inactivate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 15 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression, such as described for the disruption of ApoE in mice (Plump *et al.*, 1992, *Cell* 71: 343-353).

[00229] The host cells of the invention can also be used to produce non-human

20 transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 25 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -coding sequences have been introduced.

Such host cells can then be used to create non-human transgenic animals in which exogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 30 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequences have been introduced into their genome or homologous recombinant animals in which endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656,

32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or
5 6585 sequences have been altered. Such animals are useful for studying the function and/or activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208,
10 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 and for identifying and/or evaluating modulators of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,
15 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats,
20 chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more
25 preferably a mouse, in which an endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,
30 2252, 3474, 9792, 15400, 1452 or 6585 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

[00230] A transgenic animal used in the methods of the invention can be created by introducing a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 5 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The 1682, 6169, 6193, 7771, 14395, 29002, 33216, 10 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 cDNA sequence can be introduced as a transgene into the 15 genome of a non-human animal. Alternatively, a nonhuman homologue of a human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 20 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, such as a mouse or rat 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 25 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, can be used as a transgene. Alternatively, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 30 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene homologue, such as another 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 family member, can be isolated based on hybridization to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 cDNA sequences and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 transgene to direct expression of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 transgene in its genome and/or expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036,

16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA in tissues or cells of the animals. A transgenic founder
 5 animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,
 10 2252, 3474, 9792, 15400, 1452 or 6585 protein can further be bred to other transgenic animals carrying other transgenes.

[00231] To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726,
 15 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene into which a deletion, addition or substitution has been
 20 introduced to thereby alter, *e.g.*, functionally disrupt, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,
 25 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene. The 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,
 30 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene can be a human gene but more preferably, is a non-human homologue of a human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799,

26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene. For example, a rat 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene can be used to construct a homologous recombination nucleic acid molecule, *e.g.*, a vector, suitable for altering an endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene in the mouse genome. In a preferred embodiment, the homologous recombination nucleic acid molecule is designed such that, upon homologous recombination, the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the homologous recombination nucleic acid molecule can be designed such that, upon homologous recombination, the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,

2252, 3474, 9792, 15400, 1452 or 6585 protein). In the homologous recombination nucleic acid molecule, the altered portion of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene to allow for homologous recombination to occur between the exogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene carried by the homologous recombination nucleic acid molecule and an endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene in a cell, *e.g.*, an embryonic stem cell. The additional flanking 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the homologous recombination nucleic acid molecule (see, *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The homologous

recombination nucleic acid molecule is introduced into a cell, *e.g.*, an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene has homologously recombined with the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells can then be injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination nucleic acid molecules, *e.g.*, vectors, or homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

[00232] In another embodiment, transgenic non-human animals for use in the methods of the invention can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can

be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

[00233] Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

[00234] The 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 transgenic animals that express 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 peptide (detected immunocytochemically, using antibodies directed against 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

6585 epitopes) at easily detectable levels should then be further evaluated to identify those animals which display characteristic cardiovascular disease symptoms. Such cardiovascular disease symptoms may include, for example, increased prevalence and size of fatty streaks and/or cardiovascular disease plaques.

- 5 [00235] Additionally, specific cell types (*e.g.*, endothelial cells) within the transgenic animals may be analyzed and assayed for cellular phenotypes characteristic of cardiovascular disease. In the case of endothelial cells, such phenotypes include, but are not limited to cell proliferation, migration, angiogenesis, production of proinflammatory growth factors and cytokines, and adhesion to inflammatory cells. In the case of
- 10 monocytes, such phenotypes may include but are not limited to increases in rates of LDL uptake, adhesion to endothelial cells, transmigration, foam cell formation, fatty streak formation, and production of foam cell specific products. Cellular phenotypes may include a particular cell type's pattern of expression of genes associated with cardiovascular disease as compared to known expression profiles of the particular cell type
- 15 in animals exhibiting cardiovascular disease symptoms.

Cell-Based Systems

- [00236] Cells that contain and express 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207,
- 20 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences which encode a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491,
- 25 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, and, further, exhibit cellular phenotypes associated with cardiovascular disease, may be used to identify compounds
- 30 that exhibit anti-cardiovascular disease activity. Such cells may include non-recombinant monocyte cell lines, such as U937 (ATCC# CRL-1593), THP-1 (ATCC#TIB-202), and P388D1 (ATCC# TIB-63); endothelial cells such as human umbilical vein endothelial cells (HUVECs), human microvascular endothelial cells (HMVEC), and bovine aortic endothelial cells (BAECs); as well as generic mammalian cell lines such as HeLa cells and

COS cells, e.g., COS-7 (ATCC# CRL-1651). Further, such cells may include recombinant, transgenic cell lines. For example, the cardiovascular disease animal models of the invention, discussed above, may be used to generate cell lines, containing one or more cell types involved in cardiovascular disease, that can be used as cell culture models for this disorder. While primary cultures derived from the cardiovascular disease transgenic animals of the invention may be utilized, the generation of continuous cell lines is preferred. For examples of techniques which may be used to derive a continuous cell line from the transgenic animals, see Small *et al.*, (1985) *Mol. Cell Biol.* 5:642-648.

[00237] Alternatively, cells of a cell type known to be involved in cardiovascular disease may be transfected with sequences capable of increasing or decreasing the amount of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression within the cell. For example, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences may be introduced into, and overexpressed in, the genome of the cell of interest, or, if endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences are present, they may be either overexpressed or, alternatively disrupted in order to underexpress or inactivate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression.

[00238] In order to overexpress a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, the coding portion of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene may be ligated to a regulatory sequence which is capable of driving gene expression in the cell type of interest, *e.g.*, an endothelial cell. Such regulatory regions will be well known to those of skill in the art, and may be utilized in the absence of undue experimentation. Recombinant methods for expressing target genes are described above.

[00239] For underexpression of an endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequence, such a sequence may be isolated and engineered such that when reintroduced into the genome of the cell type of interest, the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 alleles will be inactivated. Preferably, the engineered 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence is introduced via gene targeting such that the endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726,

69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence is disrupted upon integration of the engineered 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence into the cell's genome. Transfection of host cells with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 genes is discussed, above.

[00240] Cells treated with compounds or transfected with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 genes can be examined for phenotypes associated with cardiovascular disease. In the case of monocytes, such phenotypes include but are not limited to increases in rates of LDL uptake, adhesion to endothelial cells, transmigration, foam cell formation, fatty streak formation, and production by foam cells of growth factors such as bFGF, IGF-I, VEGF, IL-1, M-CSF, TGF β , TGF α , TNF α , HB-EGF, PDGF, IFN- γ , and GM-CSF. Transmigration rates, for example, may be measured using the in vitro system of Navab *et al.* (1988) *J. Clin. Invest.* 82:1853-1863, by quantifying the number of monocytes that migrate across the endothelial monolayer and into the collagen layer of the subendothelial space.

[00241] Similarly, endothelial cells can be treated with test compounds or transfected with genetically engineered 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532,

18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 genes. The endothelial cells can then be examined for phenotypes associated with cardiovascular disease, including, but not limited to changes in cellular morphology, cell proliferation, cell migration, and mononuclear cell adhesion; or for the effects on production of other proteins involved in cardiovascular disease such as adhesion molecules (*e.g.*, ICAM, VCAM, E-selectin), growth factors and cytokines (*e.g.*, PDGF, IL-1 β , TNF α , MCF), and proteins involved in angiogenesis (*e.g.*, FLK, FLT).

[00242] Transfection of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid may be accomplished by using standard techniques (described in, for example, Ausubel (1989) *supra*). Transfected cells should be evaluated for the presence of the recombinant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences, for expression and accumulation of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA, and for the presence of recombinant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein production. In instances wherein a decrease in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484,

345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression is desired, standard techniques may be used to demonstrate whether a decrease in endogenous 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression and/or in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein production is achieved.

[00243] Cellular models for the study of cardiovascular disease and angiogenesis include models of endothelial cell differentiation on Matrigel (Baatout, S. *et al.* (1996) *Rom. J. Intern. Med.* 34:263-269; Benelli, R *et al.* (1999) *Int. J. Biol. Markers* 14:243-246), embryonic stem cell models of vascular morphogenesis (Doetschman, T. *et al.* (1993) *Hypertension* 22:618-629), the culture of microvessel fragments in physiological gels (Hoying, JB *et al.* (1996) *In Vitro Cell Dev. Biol. Anim.* 32: 409-419; US Patent No. 5,976,782), and the treatment of endothelial cells and smooth muscle cells with atherogenic and angiogenic factors including growth factors and cytokines (e.g., IL-1 β , PDGF, TNF α , VEGF), homocysteine, and LDL. *In vitro* angiogenesis models are described in, for example, Black, AF *et al.* (1999) *Cell Biol. Toxicol.* 15:81-90.

Predictive Medicine:

[00244] The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445,

64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein and/or nucleic acid expression as well as 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, in the context of a biological sample (e.g., blood, serum, cells, e.g., endothelial cells, or tissue, e.g., vascular tissue) to thereby determine whether an individual is afflicted with a cardiovascular disease. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a cardiovascular disorder. For example, mutations in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene can be assayed for in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a cardiovascular disorder, e.g., atherosclerosis.

[00245] Another aspect of the invention pertains to monitoring the influence of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulators (e.g., anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165,

2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ribozymes) on the expression or activity of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 in clinical trials.

[00246] These and other agents are described in further detail in the following sections.

Diagnostic Assays For Cardiovascular Disease

[00247] To determine whether a subject is afflicted with a cardiovascular disease, a biological sample may be obtained from a subject and the biological sample may be contacted with a compound or an agent capable of detecting a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or nucleic acid (*e.g.*, mRNA or genomic DNA) that encodes a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, in the biological sample. A preferred agent for detecting 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484,

345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or genomic DNA. The nucleic acid probe can be, for example, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid set forth in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 35, 40, 45, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

[00248] A preferred agent for detecting 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein in a sample is an antibody capable of binding to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or

F(ab')₂ can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

[00249] The term "biological sample" is intended to include tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present within a subject. That is, the detection method of the invention can be used to detect 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 genomic DNA

include Southern hybridizations. Furthermore, *in vivo* techniques for detection of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein include introducing into a subject a labeled anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

15. [00250] In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA, or genomic DNA, such that the presence of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA or genomic DNA in the control sample with the presence of 1682, 6169, 6193,

7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA or genomic DNA in the test sample.

Prognostic Assays For Cardiovascular Disease

[00251] The present invention further pertains to methods for identifying subjects having or at risk of developing a cardiovascular disease associated with aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity.

[00252] As used herein, the term "aberrant" includes a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity which deviates from the wild type 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does not follow the wild type developmental pattern of expression or the subcellular pattern of expression. For example, aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135,

12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity is intended to include the cases in which a mutation in the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene causes the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene to be under-expressed or over-expressed and situations in which such mutations result in a non-functional 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or a protein which does not function in a wild-type fashion, *e.g.*, a protein which does not interact with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate, or one which interacts with a non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate.

[00253] The assays described herein, such as the preceding diagnostic assays or the following assays, can be used to identify a subject having or at risk of developing a cardiovascular disease, *e.g.*, including but not limited to, atherosclerosis, ischemia/reperfusion injury, hypertension, restenosis, arterial inflammation, and

endothelial cell disorders. A biological sample may be obtained from a subject and tested for the presence or absence of a genetic alteration. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 2) an addition of one or more nucleotides to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 3) a substitution of one or more nucleotides of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 4) a chromosomal rearrangement of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 5) an alteration in the level of a messenger RNA transcript of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 6) aberrant modification of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686,

43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, 8) a non-wild type level of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -protein, 9) allelic loss of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, and 10) inappropriate post-translational modification of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -protein.

[00254] As described herein, there are a large number of assays known in the art which can be used for detecting genetic alterations in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene. For example, a genetic alteration in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,

8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene may be detected using a probe/primer in a polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method includes collecting a biological sample from a subject, isolating nucleic acid (*e.g.*, genomic DNA, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene under conditions such that hybridization and amplification of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[00255] Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or

any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

5 [00256] In an alternative embodiment, mutations in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 10 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene from a biological sample can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA 15 indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

[00257] In other embodiments, genetic mutations in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 20 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be identified by hybridizing biological sample derived and control nucleic acids, e.g., DNA or RNA, to high density arrays 25 containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7:244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 30 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al.* (1996) *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a

sample and control to identify base changes between the sequences by making linear arrays of sequential, overlapping probes. This step allows for the identification of point mutations. This step is followed by a second hybridization array that allows for the characterization of specific mutations by using smaller, specialized probe arrays

5 complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

[00258] In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the 1682, 6169, 6193, 7771, 14395, 10 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene in a biological sample and detect 15 mutations by comparing the sequence of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 20 2252, 3474, 9792, 15400, 1452 or 6585 in the biological sample with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert (1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger (1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the 25 diagnostic assays (Naeve, C. W. (1995) *Biotechniques* 19:448-53), including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

[00259] Other methods for detecting mutations in the 1682, 6169, 6193, 30 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene include methods in which

protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397 and Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

[00260] In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662).

According to an exemplary embodiment, a probe based on a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345,

9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence, *e.g.*, a wild-type 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 5 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

[00261] In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 15 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144 and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 25 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. 30 The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded

heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

[00262] In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to ensure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

[00263] Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

[00264] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

[00265] Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator (*e.g.*, an agonist, antagonist, peptidomimetic; protein, peptide, nucleic acid, or small molecule) to effectively treat a cardiovascular disease, *e.g.*, atherosclerosis.

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Monitoring of Effects During Clinical Trials

[00266] The present invention further provides methods for determining the effectiveness of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator identified herein) in treating a cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis, in a subject. For example, the effectiveness of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator in increasing 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585

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gene expression, protein levels, or in upregulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, can be monitored in clinical trials of subjects exhibiting decreased 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression, protein levels, or downregulated 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. Alternatively, the effectiveness of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator in decreasing 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression, protein levels, or in downregulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, can be monitored in clinical trials of subjects exhibiting increased 1682, 6169, 6193, 7771, 14395,

29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression, protein levels, or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. In such clinical trials, the expression or activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, and preferably, other genes that have been implicated in, for example, atherosclerosis and/or thrombosis can be used as a "read out" or marker of the phenotype of a particular cell, *e.g.*, a vascular endothelial cell.

[00267] For example, and not by way of limitation, genes, including 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585, that are modulated in cells by treatment with an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents which modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,

8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity on subjects suffering from a cardiovascular disease in, for example, a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 and other genes implicated in the cardiovascular disease. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods described herein, or by measuring the levels of activity of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. This response state may be determined before, and at various points during treatment of the individual with the agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity.

[00268]

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747,

1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity (e.g.,
5 an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105,
10 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA, or genomic DNA in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the
15 level of expression or activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792,
20 15400, 1452 or 6585 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,
25 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA, or genomic DNA in the pre-administration sample with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610,
30 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression

or activity of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an embodiment, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

Methods of Treatment of Subjects Suffering From Cardiovascular Disease:

[00269] The present invention provides for both prophylactic and therapeutic methods of treating a subject, *e.g.*, a human, at risk of (or susceptible to) a cardiovascular disease such as atherosclerosis, ischemia/reperfusion injury, hypertension, restenosis, arterial inflammation, thrombosis, and endothelial cell disorders. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics. "Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers to the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype").

[00270] Thus, another aspect of the invention provides methods for tailoring an subject's prophylactic or therapeutic treatment with either the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecules of the present invention or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

Prophylactic Methods

[00271] In one aspect, the invention provides a method for preventing in a subject, a cardiovascular disease by administering to the subject an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, *e.g.*, modulation of calcium influx, cellular migration, or formation of atherosclerotic lesions. Subjects at risk for a cardiovascular disease, *e.g.*, atherosclerosis and/or thrombosis, can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of a prophylactic agent can occur prior to the

manifestation of symptoms characteristic of aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity, such that a cardiovascular disease is prevented or, alternatively, delayed in its progression.

Depending on the type of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 aberrancy, for example, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 , 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 agonist or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

30

Therapeutic Methods

[00272] Described herein are methods and compositions whereby cardiovascular disease symptoms may be ameliorated. Certain cardiovascular diseases are brought about, at least in part, by an excessive level of a gene product, or by the presence of a gene

product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of cardiovascular disease symptoms. Techniques for the reduction of gene expression levels or the activity of a protein are discussed below.

5 [00273] Alternatively, certain other cardiovascular diseases are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a protein's activity. As such, an increase in the level of gene expression and/or the activity of such proteins would bring about the amelioration of cardiovascular disease symptoms.

10 [00274] In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a gene's expression, or the activity of the gene product, will reinforce the protective effect it exerts. Some cardiovascular disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of
15 gene expression and/or the activity of such gene products would bring about the amelioration of cardiovascular disease symptoms. Techniques for increasing target gene expression levels or target gene product activity levels are discussed herein.

[00275] Accordingly, another aspect of the invention pertains to methods of modulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427,
20 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity for therapeutic purposes. Accordingly, in an exemplary
25 embodiment, the modulatory method of the invention involves contacting a cell with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489,
30 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 or agent that modulates one or more of the activities of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686,

43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein activity associated with the cell (e.g., an endothelial cell or an ovarian cell). An agent that modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein (e.g., a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ligand or substrate), a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibody, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 agonist or antagonist, a peptidomimetic of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792,

15400, 1452 or 6585 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activities. Examples of such stimulatory agents include active 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein and a nucleic acid molecule encoding 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 that has been introduced into the cell. In another embodiment, the agent inhibits one or more 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activities. Examples of such inhibitory agents include antisense 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules, anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies, and 1682,

6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 inhibitors. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity. In another embodiment, the method involves administering a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity.

[00276] Stimulation of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is desirable in situations in which 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 is abnormally downregulated and/or in which increased 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is likely to have a beneficial effect. Likewise, inhibition of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is desirable in situations in which 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 is abnormally upregulated and/or in which decreased 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is likely to have a beneficial effect.

Methods for Inhibiting Target Gene Expression, Synthesis, or Activity

[00277] As discussed above, genes involved in cardiovascular disorders may cause such disorders via an increased level of gene activity. In some cases, such up-regulation may have a causative or exacerbating effect on the disease state. A variety of techniques
5 may be used to inhibit the expression, synthesis, or activity of such genes and/or proteins.

[00278] For example, compounds such as those identified through assays described above, which exhibit inhibitory activity, may be used in accordance with the invention to ameliorate cardiovascular disease symptoms. Such molecules may include, but are not limited to, small organic molecules, peptides, antibodies, and the like.

10 [00279] For example, compounds can be administered that compete with endogenous ligand for the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. The resulting reduction in the amount of ligand-bound 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 20 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein will modulate endothelial cell physiology. Compounds that can be particularly useful for this purpose include, for example, soluble proteins or peptides, such as peptides comprising one or more of the extracellular domains, or portions and/or analogs thereof, of the 1682, 6169, 25 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, including, for 30 example, soluble fusion proteins such as Ig-tailed fusion proteins. (For a discussion of the production of Ig-tailed fusion proteins, see, for example, U.S. Pat. No. 5,116,964).

Alternatively, compounds, such as ligand analogs or antibodies, that bind to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856,

32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 receptor site, but do not activate the protein, (*e.g.*, receptor-ligand antagonists) can be effective in inhibiting
 5 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein
 10 activity.

[00280] Further, antisense and ribozyme molecules which inhibit expression of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene may also be used in accordance with the invention to inhibit aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene activity. Still further, triple helix molecules may be utilized in inhibiting aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene activity.

[00281] The antisense nucleic acid molecules used in the methods of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

[00282] In yet another embodiment, an antisense nucleic acid molecule used in the methods of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

[00283] In still another embodiment, an antisense nucleic acid used in the methods of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

6585 mRNA transcripts to thereby inhibit translation of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA. A ribozyme having specificity for a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding nucleic acid can be designed based upon the nucleotide sequence of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125.) For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding mRNA (see, for example, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA can be used to select a catalytic RNA having a specific

ribonuclease activity from a pool of RNA molecules (see, for example, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418).

[00284] 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression can also be inhibited by targeting nucleotide sequences

complementary to the regulatory region of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 (e.g., the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 promoter and/or enhancers) to form triple helical

structures that prevent transcription of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene in target cells (see, for example, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15).

[00285] Antibodies that are both specific for the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein and interfere with its activity may also be used to modulate or inhibit 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726,

69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein function. Such antibodies may be generated using standard techniques described herein, against the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein itself or against peptides corresponding to portions of the protein. Such antibodies include but are not limited to polyclonal, monoclonal, Fab fragments, single chain antibodies, or chimeric antibodies.

[00286] In instances where the target gene protein is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin liposomes may be used to deliver the antibody or a fragment of the Fab region which binds to the target epitope into cells. Where fragments of the antibody are used, the smallest inhibitory [00287] fragment which binds to the target protein's binding domain is preferred. For example, peptides having an amino acid sequence corresponding to the domain of the variable region of the antibody that binds to the target gene protein may be used. Such peptides may be synthesized chemically or produced via recombinant DNA technology using

[00288] methods well known in the art (described in, for example, Creighton (1983), *supra*; and Sambrook *et al.* (1989) *supra*). Single chain neutralizing antibodies which bind to intracellular target gene epitopes may also be administered. Such single chain antibodies may be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:7889-7893).

[00289] In some instances, the target gene protein is extracellular, or is a transmembrane protein, such as the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848,

32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Antibodies that are specific for one or more extracellular domains of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, for example, and that interfere with its activity, are particularly useful in treating cardiovascular disease. Such antibodies are especially efficient because they can access the target domains directly from the bloodstream. Any of the administration techniques described below which are appropriate for peptide administration may be utilized to effectively administer inhibitory target gene antibodies to their site of action.

Methods for Restoring or Enhancing Target Gene Activity

[00290] Genes that cause cardiovascular disease may be underexpressed within cardiovascular disease situations. Alternatively, the activity of the protein products of such genes may be decreased, leading to the development of cardiovascular disease symptoms. Such down-regulation of gene expression or decrease of protein activity might have a causative or exacerbating effect on the disease state.

[00291] In some cases, genes that are up-regulated in the disease state might be exerting a protective effect. A variety of techniques may be used to increase the expression, synthesis, or activity of genes and/or proteins that exert a protective effect in response to cardiovascular disease conditions.

[00292] Described in this section are methods whereby the level 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity may be increased to levels wherein cardiovascular disease symptoms are ameliorated. The level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590,

15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity may be increased, for example, by either increasing the level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 5 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene expression or by increasing the level of active 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 10 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein which is present.

[00293] For example, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, at a level sufficient to ameliorate cardiovascular disease 20 symptoms may be administered to a patient exhibiting such symptoms. Any of the techniques discussed below may be used for such administration. One of skill in the art will readily know how to determine the concentration of effective, non-toxic doses of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, 25 utilizing techniques such as those described below.

[00294] Additionally, RNA sequences encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein may be directly administered to a 30

patient exhibiting cardiovascular disease symptoms, at a concentration sufficient to produce a level of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein such that cardiovascular disease symptoms are ameliorated. Any of the techniques discussed below, which achieve intracellular administration of compounds, such as, for example, liposome administration, may be used for the administration of such RNA molecules. The RNA molecules may be produced, for example, by recombinant techniques such as those described herein.

[00295] Further, subjects may be treated by gene replacement therapy. One or more copies of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene, or a portion thereof, that directs the production of a normal 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein with 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 function, may be inserted into cells using vectors which include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes. Additionally, techniques such as those described above may be used for the introduction of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448,

2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene sequences into human cells.

[00296] Cells, preferably, autologous cells, containing 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expressing gene sequences may then be introduced or reintroduced into the subject at positions which allow for the amelioration of cardiovascular disease symptoms. Such cell replacement techniques may be preferred, for example, when the gene product is a secreted, extracellular gene product.

Pharmaceutical Compositions

[00297] Another aspect of the invention pertains to methods for treating a subject suffering from a cardiovascular disease, *e.g.*, atherosclerosis. These methods involve administering to a subject an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity (*e.g.*, an agent identified by a screening assay described herein), or a combination of such agents. In another embodiment, the method involves administering to a subject a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 expression or activity.

[00298] Stimulation of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is desirable in situations in which 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 is abnormally downregulated and/or in which increased 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is likely to have a beneficial effect. Likewise, inhibition of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is desirable in situations in which 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 is abnormally upregulated and/or in which decreased 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,

2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity is likely to have a beneficial effect, *e.g.*, inhibition of atherosclerotic lesion formation.

[00299] The agents which modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 5 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity can be administered to a subject using pharmaceutical compositions suitable for such administration. Such compositions 10 typically comprise the agent (*e.g.*, nucleic acid molecule, protein, or antibody) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for 15 pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00300] A pharmaceutical composition used in the therapeutic methods of 20 the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for 25 injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted 30 with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00301] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the

extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00302] Sterile injectable solutions can be prepared by incorporating the agent that modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity (*e.g.*, a fragment of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or an anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474,

9792, 15400, 1452 or 6585 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required
5 other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00303] Oral compositions generally include an inert diluent or an edible
10 carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

15 Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant
20 such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00304] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable
25 propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[00305] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts,
30 and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00306] The agents that modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00307] In one embodiment, the agents that modulate 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[00308] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the agent that modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448,

2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

5 [00309] Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD50/ED50.

10 Agents which exhibit large therapeutic indices are preferred. While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[00310] The data obtained from the cell culture assays and animal studies
15 can be used in formulating a range of dosage for use in humans. The dosage of such 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833,
20 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulating agents lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any agent used in the therapeutic methods of the invention, the therapeutically effective dose can be estimated initially from
25 cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid
30 chromatography.

[00311] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4

to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[00312] In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

[00313] The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

[00314] Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5

milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). It is

[00315] Furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[00316] Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[00317] The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin

such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[00318] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[00319] The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see, *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

Pharmacogenomics

[00320] In conjunction with the therapeutic methods of the invention, pharmacogenomics (*i.e.*, the study of the relationship between a subject's genotype and that

subject's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug.

Thus, a physician or clinician may consider applying knowledge obtained in relevant

5 pharmacogenomics studies in determining whether to administer an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 10 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity, as well as tailoring the dosage and/or therapeutic regimen of treatment with an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 15 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity.

[00321] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in 20 affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11): 983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body 25 acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate aminopeptidase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of 30 fava beans.

[00322] One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or

variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

[00323] Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug target is known (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein used in the methods of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[00324] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and the cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is

highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

[00325] Alternatively, a method termed the "gene expression profiling" can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecule or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator used in the methods of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

[00326] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of a subject. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and, thus, enhance therapeutic or prophylactic efficiency when treating a subject suffering from a cardiovascular disease, *e.g.*, atherosclerosis, with an agent which modulates 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity.

Recombinant Expression Vectors and Host Cells Used in the Methods of the Invention

[00327] The methods of the invention (*e.g.*, the screening assays described herein) include the use of vectors, preferably expression vectors, containing a nucleic acid encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[00328] The recombinant expression vectors to be used in the methods of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host

cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel (1990) *Methods Enzymol.* 185:3-7.

Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins, mutant forms of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins, fusion proteins, and the like).

[00329]

The recombinant expression vectors to be used in the methods of the invention can be designed for expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins in prokaryotic or eukaryotic cells. For example, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins can be

expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel (1990) *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[00330] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[00331] Purified fusion proteins can be utilized in 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins. In a preferred embodiment, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105,

38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six weeks).

[00332] In another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual*. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

[00333] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid).

[00334] The methods of the invention may further use a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific, or cell type specific expression of antisense RNA. The

antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

[00335] Another aspect of the invention pertains to the use of host cells into which a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecule of the invention is introduced, *e.g.*, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecule within a recombinant expression vector or a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecule containing sequences which allow it to homologously recombine into a specific site of the host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[00336] A host cell can be any prokaryotic or eukaryotic cell. For example, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,

8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[00337] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

[00338] A host cell used in the methods of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Accordingly, the invention further provides methods for producing a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein has been introduced) in a suitable medium

such that a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein is produced. In another embodiment, the method further comprises isolating a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein from the medium or the host cell.

Isolated Nucleic Acid Molecules Used in the Methods of the Invention

15 [00339] The methods of the invention include the use of isolated nucleic acid molecules that encode 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 20 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 25 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding nucleic acid molecules (e.g., 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA) and fragments for use as PCR primers for the amplification or mutation of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491,

1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules. As used
5 herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

[00340]

A nucleic acid molecule used in the methods of the present
10 invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information
15 provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125 as a hybridization probe, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747,
20 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as
25 described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

[00341]

Moreover, a nucleic acid molecule encompassing all or a portion of
SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43,
30 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71,

73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125.

[00342] A nucleic acid used in the methods of the invention can be amplified using cDNA, mRNA or, alternatively, genomic DNA as a template and appropriate

5 oligonucleotide primers according to standard PCR amplification techniques. Furthermore, oligonucleotides corresponding to 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 10 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

[00343] In a preferred embodiment, the isolated nucleic acid molecules used in the methods of the invention comprise the nucleotide sequence shown in SEQ ID NO:1,

15 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, a complement of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 20 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 25 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125 is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, such that it can hybridize to the nucleotide 30 sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, thereby forming a stable duplex.

[00344] In still another preferred embodiment, an isolated nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, or a portion of any of this nucleotide sequence.

[00345] Moreover, the nucleic acid molecules used in the methods of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, *e.g.*, a biologically active portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, of an anti-sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113,

115, 117, 119, 121, 123 or 125, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125. In one
5 embodiment, a nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is greater than 100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, 1200-1300, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21,
10 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125.

[00346] As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide
15 sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent
20 conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7, 9 and 11. A preferred, non-limiting example of stringent hybridization conditions includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or
25 hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly stringent hybridization conditions includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced
30 stringency hybridization conditions includes hybridization in 4X SSC, at about 50-60°C (or alternatively hybridization in 6X SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, e.g., at 65-70°C or at 42-50°C are also intended to be encompassed by the

present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(^{\circ}\text{C}) = 2(\# \text{ of A} + \text{T bases}) + 4(\# \text{ of G} + \text{C bases})$. For hybrids between 18¹ and 49 base pairs in length, $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\% \text{G} + \text{C}) - (600/\text{N})$, where N is the number of bases in the hybrid, and $[\text{Na}^+]$ is the concentration of sodium ions in the hybridization buffer ($[\text{Na}^+]$ for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M NaH₂PO₄, 7% SDS at about 65°C, followed by one or more washes at 0.02M NaH₂PO₄, 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

[00347]

In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, such as by measuring a level of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding nucleic acid

in a sample of cells from a subject *e.g.*, detecting 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA levels or determining whether a genomic 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 gene has been mutated or deleted.

[00348]

The methods of the invention further encompass the use of nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, due to degeneracy of the genetic code and thus encode the same 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125. In another embodiment, an isolated nucleic acid molecule included in the methods of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126.

[00349]

The methods of the invention further include the use of allelic variants of human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650,

14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585, *e.g.*, functional and non-functional allelic variants. Functional allelic variants are naturally occurring amino acid sequence variants of the human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein that maintain a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

[00350] Non-functional allelic variants are naturally occurring amino acid sequence variants of the human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein that do not have a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. Non-functional allelic variants will typically contain a non-conservative substitution, deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22,

24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126, or a substitution, insertion or deletion in critical residues or critical regions of the protein.

5 [00351] The methods of the present invention may further use non-human orthologues of the human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 10 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Orthologues of the human 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 15 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein are proteins that are isolated from non-human organisms and possess the same 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 20 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity.

[00352] The methods of the present invention further include the use of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 25 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, or a portion thereof, in which a mutation has been introduced. The mutation may lead to amino acid substitutions at "non-essential" amino acid residues or at "essential" amino acid residues. A "non-essential" 30 amino acid residue is a residue that can be altered from the wild-type sequence of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833,

2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 (*e.g.*, the sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126) without
 5 altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912,
 10 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins of the present invention and other members of the family are not likely to be amenable to alteration.

[00353] Mutations can be introduced into SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61,
 15 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced
 20 with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side
 25 chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or

part of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585
 5 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445,
 10 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95,
 15 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using the assay described herein.

[00354] Another aspect of the invention pertains to the use of isolated nucleic acid molecules which are antisense to the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123 or 125. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656,

32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (also referred to as 5' and 3' untranslated regions).

[00355] Given the coding strand sequences encoding 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792,

15400, 1452 or 6585 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxymethylaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Antisense nucleic acid molecules used in the methods of the invention are further described above, in section IV.

[00356] In yet another embodiment, the 139, 258, 1261, 1486, 2398, 2414, 7660, 8587, 10183, 10550, 12680, 17921, 32248, 60489 or 93804 nucleic acid molecules used in the methods of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci.* 93:14670-675.

[00357] PNAs of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules can be used in the therapeutic and diagnostic applications described herein. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. *et al.* (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *supra*).

[00358] In another embodiment, PNAs of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. *et al.* (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. *et al.* (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

[00359] In other embodiments, the oligonucleotide used in the methods of the invention may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W088/09810) or the blood-

brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*,
 5 a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

Isolated 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445,
 10 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585
Proteins and Anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650,
 15 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208,
2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or
6585 Antibodies Used in the Methods of the Invention

[00360] The methods of the invention include the use of isolated 1682, 6169, 6193,
 20 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins, and biologically active
 25 portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130,
 30 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies. In one embodiment, native 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686,

43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

[00361]

As used herein, a "biologically active portion" of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein includes a fragment of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein having a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity. Biologically active portions of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207,

1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126 which include fewer amino acids than the full length 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins, and exhibit at least one activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein (*e.g.*, the N-terminal region of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein that is believed to be involved in the regulation of apoptotic activity). A biologically active portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be a polypeptide which is, for example, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300 or more amino acids in length. Biologically active portions of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be used as targets for developing agents which modulate a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 activity.

[00362] In a preferred embodiment, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein used in the methods of the invention has an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126. In other embodiments, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein is substantially identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126, and retains the functional activity of the protein of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection V above. Accordingly, in another embodiment, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein used in the methods of the invention is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126.

[00363] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

6585 amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126, having 500 amino acid residues, at least 75, preferably at least 150, more preferably at least 225, even more preferably at least 300, and even more preferably at least 400 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[00364] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.* 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[00365] The methods of the invention may also use 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 chimeric or fusion proteins. As used

herein, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 "chimeric protein" or "fusion protein" comprises a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide operatively linked to a non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide. An "1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecule, whereas a "non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 1682, 6169, 6193, 7771, 14395,

29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, *e.g.*, a protein which is different from the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein and which is derived from the same or a different organism. Within a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion protein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide can correspond to all or a portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. In a preferred embodiment, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion protein comprises at least one biologically active portion of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036,

16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. In another preferred embodiment, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion protein comprises at least two biologically active portions of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide and the non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide are fused in-frame to each other. The non-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide can be fused to the N-terminus or C-terminus of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135,

10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide.

[00366] For example, in one embodiment, the fusion protein is a GST-1682,
5 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion protein in
10 which the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585
15 sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686,
20 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 .

[00367] In another embodiment, this fusion protein is a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484,
25 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726,
30 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be increased through use of a heterologous signal sequence.

[00368] The 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion proteins used in the methods of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion proteins can be used to affect the bioavailability of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate. Use of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fusion proteins may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein; (ii) mis-regulation of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474,

9792, 15400, 1452 or 6585 gene; and (iii) aberrant post-translational modification of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein.

[00369] Moreover, the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -fusion proteins used in the methods of the invention can be used as immunogens to produce anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies in a subject, to purify 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 ligands and in screening assays to identify molecules which inhibit the interaction of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 substrate.

[00370] Preferably, a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 chimeric or fusion protein used in the methods of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein.

[00371] The present invention also pertains to the use of variants of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,

8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins which function as either 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 agonists (mimetics) or as 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antagonists. Variants of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. An agonist of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833,

2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. An antagonist of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can inhibit one or more of the activities of the naturally occurring form of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein by, for example, competitively modulating a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 -mediated activity of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein.

[00372]

In one embodiment, variants of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077,

33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein which function as either 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 agonists (mimetics) or as 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein for 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein agonist or antagonist activity. In one embodiment, a variegated library of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077,

33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequences therein. There are a variety of methods which can be used to produce libraries of potential 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (*see, e.g.*,

Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

[00373] In addition, libraries of fragments of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein coding sequence can be used to generate a variegated population of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 fragments for screening and subsequent selection of variants of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135,

10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein.

[00374] Several techniques are known in the art for screening gene products

5 of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 10 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression 15 vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to 20 identify 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 25 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

[00375] The methods of the present invention further include the use of anti-

1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 30 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies. An isolated 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245,

58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein, or a portion or fragment thereof, can be used as an immunogen to generate

5 antibodies that bind 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

10 6585 using standard techniques for polyclonal and monoclonal antibody preparation. A full-length 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914,

15 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein can be used or, alternatively, antigenic peptide fragments of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554,

20 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be used as immunogens. The antigenic peptide of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448,

25 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94,

30 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124 or 126, and encompasses an epitope of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135,

12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 such that an antibody raised against the peptide forms a specific immune complex with the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

[00376] Preferred epitopes encompassed by the antigenic peptide are regions of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

[00377] A 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 immunogen is typically used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse, or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein or a chemically synthesized 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165,

2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent.

- 5 Immunization of a suitable subject with an immunogenic 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 preparation induces a polyclonal anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibody response.

[00378] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecules. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a

particular epitope of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . A monoclonal antibody composition thus typically displays a single binding affinity for a particular 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein with which it immunoreacts.

[00379] Polyclonal anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies can be prepared as described above by immunizing a suitable subject with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 immunogen. The anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135,

12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 . If desired, the antibody molecules directed against 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma

producing a monoclonal antibody that binds 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 .

[00380] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* (1977) *supra*; Lerner (1981) *supra*; and Kenneth (1980) *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464,

17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585, e.g., using a standard ELISA assay.

[00381] Alternative to preparing monoclonal antibody-secreting hybridomas,

a monoclonal anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656,

5 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650,

14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448,

2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208,

2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or

6585 antibody can be identified and isolated by screening a recombinant combinatorial

10 immunoglobulin library (e.g., an antibody phage display library) with 1682, 6169, 6193,

7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491,

1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484,

345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554,

9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590,

15 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 to thereby isolate immunoglobulin

library members that bind 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292,

21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105,

38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165,

2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135,

20 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400,

1452 or 6585. Kits for generating and screening phage display libraries are commercially

available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-

01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally,

examples of methods and reagents particularly amenable for use in generating and

25 screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent

No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.*

PCT International Publication No. WO 91/17271; Winter *et al.* PCT International

Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO

92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.*

30 PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International

Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO

90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum.*

Antibod. Hybridomas 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.*

(1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et*

al. (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* (1990) *Nature* 348:552-554.

- 5 [00382] Additionally, recombinant anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,
- 10 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the methods of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in
- 15 Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986)
- 20 *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

- [00394] An anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165,
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10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 protein. Anti-1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

[00395] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figure and the Sequence Listing is incorporated herein by reference.

EXAMPLES**EXAMPLE 1: TISSUE DISTRIBUTION OF USING TAQMAN™ ANALYSIS**

[00396] This example describes the TaqMan™ procedure. The Taqman™
5 procedure is a quantitative, reverse transcription PCR-based approach for detecting
mRNA. The RT-PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold™ DNA
Polymerase to cleave a TaqMan™ probe during PCR. Briefly, cDNA was generated from
the samples of interest, *e.g.*, heart, kidney, liver, skeletal muscle, and various vessels, and
used as the starting material for PCR amplification. In addition to the 5' and 3' gene-
10 specific primers, a gene-specific oligonucleotide probe (complementary to the region being
amplified) was included in the reaction (*i.e.*, the Taqman™ probe). The TaqMan™ probe
includes the oligonucleotide with a fluorescent reporter dye covalently linked to the 5' end
of the probe (such as FAM (6-carboxyfluorescein), TET (6-carboxy-4,7,2',7'-
tetrachlorofluorescein), JOE (6-carboxy-4,5-dichloro-2,7-dimethoxyfluorescein), or VIC)
15 and a quencher dye (TAMRA (6-carboxy-N,N,N',N'-tetramethylrhodamine) at the 3' end
of the probe.

[00397] During the PCR reaction, cleavage of the probe separates the reporter dye
and the quencher dye, resulting in increased fluorescence of the reporter. Accumulation of
PCR products is detected directly by monitoring the increase in fluorescence of the
20 reporter dye. When the probe is intact, the proximity of the reporter dye to the quencher
dye results in suppression of the reporter fluorescence. During PCR, if the target of
interest is present, the probe specifically anneals between the forward and reverse primer
sites. The 5'-3' nucleolytic activity of the AmpliTaq™ Gold DNA Polymerase cleaves the
probe between the reporter and the quencher only if the probe hybridizes to the target. The
25 probe fragments are then displaced from the target, and polymerization of the strand
continues. The 3' end of the probe is blocked to prevent extension of the probe during
PCR. This process occurs in every cycle and does not interfere with the exponential
accumulation of product. RNA was prepared using the trizol method and treated with
DNase to remove contaminating genomic DNA. cDNA was synthesized using standard
30 techniques. Mock cDNA synthesis in the absence of reverse transcriptase resulted in
samples with no detectable PCR amplification of the control gene confirms efficient
removal of genomic DNA contamination.

Equivalents

[00398] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the

5 following claims.

What is claimed:

1. A method for identifying a compound capable of treating a cardiovascular disorder, comprising assaying the ability of the compound to modulate
5 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid
10 expression or 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585
15 polypeptide activity, thereby identifying a compound capable of treating a cardiovascular disorder.

2. A method for identifying a compound capable of modulating lipid production comprising:
20 a) contacting a cell which expresses 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094,
25 2252, 3474, 9792, 15400, 1452 or 6585 with a test compound; and
b) assaying the ability of the test compound to modulate the expression of a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237,
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35 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide, thereby identifying a compound capable of modulating lipid production.

3. A method for modulating lipid production in a cell comprising contacting a cell with a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator, thereby modulating lipid production in the cell.

4. The method of claim 2, wherein the cell is a hepatic cell.

5. The method of claim 3, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is a small organic molecule, peptide, antibody or antisense nucleic acid molecule.

6. The method of claim 3, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is capable of modulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide activity.

7. The method of claim 6, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is a small organic molecule, peptide, antibody or antisense nucleic acid molecule.

8. The method of claim 6, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is capable of modulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid expression.

9. A method for treating a subject having a cardiovascular disorder characterized by aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 polypeptide activity or aberrant 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 nucleic acid expression comprising administering to the subject a 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator, thereby treating said subject having a cardiovascular disorder.

10. The method of claim 9, wherein said cardiovascular disorder is selected from the group consisting of arteriosclerosis, atherosclerosis, cardiac hypertrophy, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, valvular disease, including but not limited to, valvular degeneration caused by

calcification, rheumatic heart disease, endocarditis, or complications of artificial valves; atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, pericardial disease, including but not limited to, pericardial effusion and pericarditis; cardiomyopathies, *e.g.*,
5 dilated cardiomyopathy or idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, ischemic disease, arrhythmia, sudden cardiac death, and cardiovascular developmental disorders

11. The method of claim 9, wherein said 1682, 6169, 6193, 7771,
10 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is administered in a
15 pharmaceutically acceptable formulation.

12. The method of claim 9, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252,
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13. The method of claim 9, wherein the 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992,
25 2094, 2252, 3474, 9792, 15400, 1452 or 6585 modulator is capable of modulating 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833,
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Chun, Miyoung

Galvin, Katherine M.

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Acton, Susan L.

Donoghue, Mary

Stagliano, Nancy

Perodin, Jacquelin

Rodrigue-Way, Amelie

<120> Methods and compositions for treating

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<211> 841

<212> PRT

<213> Homosapien

<400> 2

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Ser Gly Thr Val Asn Gln Ile Met Met Met Ala Asn Asn Pro Glu Asp
          35          40          45
Trp Leu Ser Leu Leu Leu Lys Leu Glu Lys Asn Ser Val Pro Leu Ser
          50          55          60
Asp Ala Leu Leu Asn Lys Leu Ile Gly Arg Tyr Ser Gln Ala Ile Glu
          65          70          75          80
Ala Leu Pro Pro Asp Lys Tyr Gly Gln Asn Glu Ser Phe Ala Arg Ile
          85          90          95
Gln Val Arg Phe Ala Glu Leu Lys Ala Ile Gln Glu Pro Asp Asp Ala
          100         105         110
Arg Asp Tyr Phe Gln Met Ala Arg Ala Asn Cys Lys Lys Phe Ala Phe
          115         120         125
Val His Ile Ser Phe Ala Gln Phe Glu Leu Ser Gln Gly Asn Val Lys
          130         135         140
Lys Ser Lys Gln Leu Leu Gln Lys Ala Val Glu Arg Gly Ala Val Pro
          145         150         155         160
Leu Glu Met Leu Glu Ile Ala Leu Arg Asn Leu Asn Leu Gln Lys Lys
          165         170         175
Gln Leu Leu Ser Glu Glu Glu Lys Lys Asn Leu Ser Ala Ser Thr Val
          180         185         190
Leu Thr Ala Gln Glu Ser Phe Ser Gly Ser Leu Gly His Leu Gln Asn
          195         200         205
Arg Asn Asn Ser Cys Asp Ser Arg Gly Gln Thr Thr Lys Ala Arg Phe
          210         215         220
Leu Tyr Gly Glu Asn Met Pro Pro Gln Asp Ala Glu Ile Gly Tyr Arg
          225         230         235         240
Asn Ser Leu Arg Gln Thr Asn Lys Thr Lys Gln Ser Cys Pro Phe Gly
          245         250         255

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Glu	Pro	Leu	Val	Ser	Asp	Glu	Lys	Ser	Ser	Glu	Leu	Ile	Ile	Thr	Asp
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Glu	Glu	Thr	Lys	Glu	Tyr	Gln	Glu	Pro	Glu	Val	Pro	Glu	Ser	Asn	Gln
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Lys	Gln	Trp	Gln	Ala	Lys	Arg	Lys	Ser	Glu	Cys	Ile	Asn	Gln	Asn	Pro
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Asn	Thr	Glu	Gln	Lys	His	Thr	Thr	Phe	Glu	Gln	Pro	Val	Phe	Ser	Val
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Ser	Lys	Gln	Ser	Pro	Pro	Ile	Ser	Thr	Ser	Lys	Trp	Phe	Asp	Pro	Lys
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Ser	Ile	Cys	Lys	Thr	Pro	Ser	Ser	Asn	Thr	Leu	Asp	Asp	Tyr	Met	Ser
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Cys	Phe	Arg	Thr	Pro	Val	Val	Lys	Asn	Asp	Phe	Pro	Pro	Ala	Cys	Gln
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Gln	Ile	Leu	Ala	Thr	Pro	Leu	Gln	Asn	Leu	Gln	Val	Leu	Ala	Ser	Ser
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Ser	Ala	Asn	Glu	Cys	Ile	Ser	Val	Lys	Gly	Arg	Ile	Tyr	Ser	Ile	Leu
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Lys	Leu	Gln	Gln	His	Ser	Asp	Lys	Ile	Ile	Arg	Leu	Tyr	Asp	Tyr	Glu
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Ile	Thr	Asp	Gln	Tyr	Ile	Tyr	Met	Val	Met	Glu	Cys	Gly	Asn	Ile	Asp
			580					585					590		
Leu	Asn	Ser	Trp	Leu	Lys	Lys	Lys	Lys	Ser	Ile	Asp	Pro	Trp	Glu	Arg
		595					600					605			
Lys	Ser	Tyr	Trp	Lys											

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Leu Leu Ala His Pro Tyr Val Gln Ile Gln Thr His Pro Val Asn Gln					
770			775		780
Met Ala Lys Gly Thr Thr Glu Glu Met Lys Tyr Val Leu Gly Gln Leu					
785			790		795
Val Gly Leu Asn Ser Pro Asn Ser Ile Leu Lys Ala Ala Lys Thr Leu					
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					815
Tyr Glu His Tyr Ser Gly Gly Glu Ser His Asn Ser Ser Ser Ser Lys					
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 <212> DNA
 <213> Homosapien

<400> 3

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 <211> 293
 <212> PRT
 <213> Homosapien

<400> 4

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 Phe Lys Asn Ala Trp Asn Tyr Met Leu Asn Asn Tyr Thr Lys Phe Gln
 35 40 45
 Ile Ala Thr Trp Gly Ser Leu Ile Val His Glu Ala Leu Tyr Phe Leu
 50 55 60
 Phe Cys Leu Pro Gly Phe Leu Phe Gln Phe Ile Pro Tyr Met Lys Lys
 65 70 75 80
 Tyr Lys Ile Gln Lys Asp Lys Pro Glu Thr Trp Glu Asn Gln Trp Lys
 85 90 95
 Cys Phe Lys Val Leu Leu Phe Asn His Phe Cys Ile Gln Leu Pro Leu
 100 105 110
 Ile Cys Gly Thr Tyr Tyr Phe Thr Glu Tyr Phe Asn Ile Pro Tyr Asp
 115 120 125
 Trp Glu Arg Met Pro Arg Trp Tyr Phe Leu Leu Ala Arg Cys Phe Gly
 130 135 140
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 145 150 155 160
 His His Lys Arg Ile Tyr Lys Tyr Ile His Lys Val His His Glu Phe
 165 170 175
 Gln Ala Pro Phe Gly Met Glu Ala Glu Tyr Ala His Pro Leu Glu Thr
 180 185 190
 Leu Ile Leu Gly Thr Gly Phe Phe Ile Gly Ile Val Leu Leu Cys Asp
 195 200 205
 His Val Ile Leu Leu Trp Ala Trp Val Thr Ile Arg Leu Leu Glu Thr
 210 215 220
 Ile Asp Val His Ser Gly Tyr Asp Ile Pro Leu Asn Pro Leu Asn Leu
 225 230 235 240
 Ile Pro Phe Tyr Ala Gly Ser Arg His His Asp Phe His His Met Asn
 245 250 255
 Phe Ile Gly Asn Tyr Ala Ser Thr Phe Thr Trp Trp Asp Arg Ile Phe
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1029

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 <213> Homosapien

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 35 40 45
 Asn Ser Leu Val Leu Val Ile Ser Ile Phe Tyr His Lys Leu Gln Ser
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 Leu Thr Asp Val Phe Leu Val Asn Leu Pro Leu Ala Asp Leu Val Phe
 65 70 75 80
 Val Cys Thr Leu Pro Phe Trp Ala Tyr Ala Gly Ile His Glu Trp Val
 85 90 95
 Phe Gly Gln Val Met Cys Lys Ser Leu Gly Ile Tyr Thr Ile Asn
 100 105 110
 Phe Tyr Thr Ser Met Leu Ile Leu Thr Cys Ile Thr Val Asp Arg Phe
 115 120 125
 Ile Val Val Val Lys Ala Thr Lys Ala Tyr Asn Gln Gln Ala Lys Arg
 130 135 140
 Met Thr Trp Gly Lys Val Thr Ser Leu Leu Ile Trp Val Ile Ser Leu
 145 150 155 160
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 180 185 190
 Ala Thr Gln Met Thr Leu Gly Phe Phe Leu Pro Leu Leu Thr Met Ile
 195 200 205
 Val Cys Tyr Ser Val Ile Ile Lys Thr Leu Leu His Ala Gly Gly Phe
 210 215 220
 Gln Lys His Arg Ser Leu Lys Ile Ile Phe Leu Val Met Ala Val Phe
 225 230 235 240
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 His Trp Glu Tyr Tyr Ala Met Thr Ser Phe His Tyr Thr Ile Met Val
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 Asp Ile Gly Cys Leu Pro Tyr Leu Gly Val Ser His Gln Trp Lys Ser
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 <212> DNA
 <213> Homosapien

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<210> 8

<211> 493

<212> PRT

<213> Homosapien

<400> 8

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 20          25          30
Leu Val Lys Gln Glu Gly Leu Arg Phe Leu Glu Gln Glu Leu Glu Thr
 35          40          45
Ile Thr Ile Pro Asp Leu Arg Gly Lys Glu Gly His Phe Tyr Tyr Asn
 50          55          60
Ile Ser Glu Val Lys Val Thr Glu Leu Gln Leu Thr Ser Ser Glu Leu
 65          70          75          80
Asp Phe Gln Pro Gln Gln Glu Leu Met Leu Gln Ile Thr Asn Ala Ser
 85          90          95
Leu Gly Leu Arg Phe Arg Arg Gln Leu Leu Tyr Trp Phe Phe Tyr Asp
100          105          110
Gly Gly Tyr Ile Asn Ala Ser Ala Glu Gly Val Ser Ile Arg Thr Gly
115          120          125
Leu Glu Leu Ser Arg Asp Pro Ala Gly Arg Met Lys Val Ser Asn Val
130          135          140
Ser Cys Gln Ala Ser Val Ser Arg Met His Ala Ala Phe Gly Gly Thr
145          150          155          160
Phe Lys Lys Val Tyr Asp Phe Leu Ser Thr Phe Ile Thr Ser Gly Met
165          170          175
Arg Phe Leu Leu Asn Gln Gln Ile Cys Pro Val Leu Tyr His Ala Gly
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Thr Val Leu Leu Asn Ser Leu Leu Asp Thr Val Pro Val Arg Ser Ser

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Val Asp Glu Leu Val Gly Ile Asp Tyr Ser Leu Met Lys Asp Pro Val		
210	215	220
Ala Ser Thr Ser Asn Leu Asp Met Asp Phe Arg Gly Ala Phe Phe Pro		
225	230	235
Leu Thr Glu Arg Asn Trp Ser Leu Pro Asn Arg Ala Val Glu Pro Gln		
245	250	255
Leu Gln Glu Glu Glu Arg Met Val Tyr Val Ala Phe Ser Glu Phe Phe		
260	265	270
Phe Asp Ser Ala Met Glu Ser Tyr Phe Arg Ala Gly Ala Leu Gln Leu		
275	280	285
Leu Leu Val Gly Asp Lys Val Pro His Asp Leu Asp Met Leu Leu Arg		
290	295	300
Ala Thr Tyr Phe Gly Ser Ile Val Leu Leu Ser Pro Ala Val Ile Asp		
305	310	315
Ser Pro Leu Lys Leu Glu Leu Arg Val Leu Ala Pro Pro Arg Cys Thr		
325	330	335
Ile Lys Pro Ser Gly Thr Thr Ile Ser Val Thr Ala Ser Val Thr Ile		
340	345	350
Ala Leu Val Pro Pro Asp Gln Pro Glu Val Gln Leu Ser Ser Met Thr		
355	360	365
Met Asp Ala Arg Leu Ser Ala Lys Met Ala Leu Arg Gly Lys Ala Leu		
370	375	380
Arg Thr Gln Leu Asp Leu Arg Arg Phe Arg Ile Tyr Ser Asn His Ser		
385	390	395
Ala Leu Glu Ser Leu Ala Leu Ile Pro Leu Gln Ala Pro Leu Lys Thr		
405	410	415
Met Leu Gln Ile Gly Val Met Pro Met Leu Asn Glu Arg Thr Trp Arg		
420	425	430
Gly Val Gln Ile Pro Leu Pro Glu Gly Ile Asn Phe Val His Glu Val		
435	440	445
Val Thr Asn His Ala Gly Phe Leu Thr Ile Gly Ala Asp Leu His Phe		
450	455	460
Ala Lys Gly Leu Arg Glu Val Ile Glu Lys Asn Arg Pro Ala Asp Val		
465	470	475
Arg Ala Ser Thr Ala Pro Thr Pro Ser Thr Ala Ala Val		
485	490	

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 <211> 1212
 <212> DNA
 <213> Homosapien

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<210> 10

<211> 403

<212> PRT

<213> Homosapien

<400> 10

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Gln Thr Glu Leu Phe Met Pro Ile Cys Ala Thr Tyr Leu Leu Ile Phe
35     40     45
Val Val Gly Ala Val Gly Asn Gly Leu Thr Cys Leu Val Ile Leu Arg
50     55     60
His Lys Ala Met Arg Thr Pro Thr Asn Tyr Tyr Leu Phe Ser Leu Ala
65     70     75     80
Val Ser Asp Leu Leu Val Leu Leu Val Gly Leu Pro Leu Glu Leu Tyr
85     90     95
Glu Met Trp His Asn Tyr Pro Phe Leu Leu Gly Val Gly Gly Cys Tyr
100    105    110
Phe Arg Thr Leu Leu Phe Glu Met Val Cys Leu Ala Ser Val Leu Asn
115    120    125
Val Thr Ala Leu Ser Val Glu Arg Tyr Val Ala Val Val His Pro Leu
130    135    140
Gln Ala Arg Ser Met Val Thr Arg Ala His Val Arg Arg Val Leu Gly
145    150    155    160
Ala Val Trp Gly Leu Ala Met Leu Cys Ser Leu Pro Asn Thr Ser Leu
165    170    175
His Gly Ile Arg Gln Leu His Val Pro Cys Arg Gly Pro Val Pro Asp
180    185    190
Ser Ala Val Cys Met Leu Val Arg Pro Arg Ala Leu Tyr Asn Met Val
195    200    205
Val Gln Thr Thr Ala Leu Leu Phe Phe Cys Leu Pro Met Ala Ile Met
210    215    220
Ser Val Leu Tyr Leu Leu Ile Gly Leu Arg Leu Arg Arg Glu Arg Leu
225    230    235    240
Leu Leu Met Gln Glu Ala Lys Gly Arg Gly Ser Ala Ala Ala Arg Ser
245    250    255
Arg Tyr Thr Cys Arg Leu Gln Gln His Asp Arg Gly Arg Arg Gln Val
260    265    270
Thr Lys Met Leu Phe Val Leu Val Val Val Phe Gly Ile Cys Trp Ala
275    280    285
Pro Phe His Ala Asp Arg Val Met Trp Ser Val Val Ser Gln Trp Thr
290    295    300
Asp Gly Leu His Leu Ala Phe Gln His Val His Val Ile Ser Gly Ile
305    310    315    320
Phe Phe Tyr Leu Gly Ser Ala Ala Asn Pro Val Leu Tyr Ser Leu Met
325    330    335
Ser Ser Arg Phe Arg Glu Thr Phe Gln Glu Ala Leu Cys Leu Gly Ala
340    345    350
Cys Cys His Arg Leu Arg Pro Arg His Ser Ser His Ser Leu Ser Arg
355    360    365
Met Thr Thr Gly Ser Thr Leu Cys Asp Val Gly Ser Leu Gly Ser Trp
370    375    380
Val His Pro Leu Ala Gly Asn Asp Gly Pro Glu Ala Gln Gln Glu Thr

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385.
Asp Pro Ser

390

395

400

<210> 11
<211> 2370
<212> DNA
<213> Homosapien

<400> 11

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2370

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<211> 431
<212> PRT
<213> Homosapien

<400> 12

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35	40	45
Cys Lys His Pro Glu Val Gln Ser Ile Leu Lys Ile Ser Gln Pro Gln		
50	55	60
Glu Pro Glu Leu Met Asn Ala Asn Pro Ser Pro Pro Pro Ser Pro Ser		
65	70	75
Gln Gln Ile Asn Leu Gly Pro Ser Ser Asn Pro His Ala Lys Pro Ser		
85	90	95
Asp Phe His Phe Leu Lys Val Ile Gly Lys Gly Ser Phe Gly Lys Val		
100	105	110
Leu Leu Ala Arg His Lys Ala Glu Glu Val Phe Tyr Ala Val Lys Val		
115	120	125
Leu Gln Lys Lys Ala Ile Leu Lys Lys Lys Glu Glu Lys His Ile Met		
130	135	140
Ser Glu Arg Asn Val Leu Leu Lys Asn Val Lys His Pro Phe Leu Val		
145	150	155
Gly Leu His Phe Ser Phe Gln Thr Ala Asp Lys Leu Tyr Phe Val Leu		
165	170	175
Asp Tyr Ile Asn Gly Gly Glu Leu Phe Tyr His Leu Gln Arg Glu Arg		
180	185	190
Cys Phe Leu Glu Pro Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ala Ser		
195	200	205
Ala Leu Gly Tyr Leu His Ser Leu Asn Ile Val Tyr Arg Asp Leu Lys		
210	215	220
Pro Glu Asn Ile Leu Leu Asp Ser Gln Gly His Ile Val Leu Thr Asp		
225	230	235
Phe Gly Leu Cys Lys Glu Asn Ile Glu His Asn Ser Thr Thr Ser Thr		
245	250	255
Phe Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu Val Leu His Lys Gln		
260	265	270
Pro Tyr Asp Arg Thr Val Asp Trp Trp Cys Leu Gly Ala Val Leu Tyr		
275	280	285
Glu Met Leu Tyr Gly Leu Pro Pro Phe Tyr Ser Arg Asn Thr Ala Glu		
290	295	300
Met Tyr Asp Asn Ile Leu Asn Lys Pro Leu Gln Leu Lys Pro Asn Ile		
305	310	315
Thr Asn Ser Ala Arg His Leu Leu Glu Gly Leu Leu Gln Lys Asp Arg		
325	330	335
Thr Lys Arg Leu Gly Ala Lys Asp Asp Phe Met Glu Ile Lys Ser His		
340	345	350
Val Phe Phe Ser Leu Ile Asn Trp Asp Asp Leu Ile Asn Lys Lys Ile		
355	360	365
Thr Pro Pro Phe Asn Pro Asn Val Ser Gly Pro Asn Glu Leu Arg His		
370	375	380
Phe Asp Pro Glu Phe Thr Glu Glu Pro Val Pro Asn Ser Ile Gly Lys		
385	390	395
Ser Pro Asp Ser Val Leu Val Thr Ala Ser Val Lys Glu Ala Ala Glu		
405	410	415
Ala Phe Leu Gly Phe Ser Tyr Ala Pro Pro Thr Asp Ser Phe Leu		
420	425	430

<210> 13

<211> 2347

<212> DNA

<213> Homosapien

<400> 13

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<210> 14

<211> 690

<212> PRT

<213> Homosapien

<400> 14

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 20          25          30
Leu Arg Trp Leu Leu Gly Asp Pro Thr Cys Cys Val Leu Leu Gly Leu
 35          40          45
Ala Met Leu Ala Arg Pro Trp Leu Gly Pro Trp Val Pro His Gly Leu
 50          55          60
Ser Leu Ala Ala Ala Ala Leu Ala Leu Thr Leu Leu Pro Ala Arg Leu
 65          70          75          80
Pro Pro Gly Leu Arg Trp Leu Pro Ala Asp Val Ile Phe Leu Ala Lys
 85          90          95
Ile Leu His Leu Gly Leu Lys Ile Arg Gly Cys Leu Ser Arg Gln Pro
100         105         110
Pro Asp Thr Phe Val Asp Ala Phe Glu Arg Arg Ala Arg Ala Gln Pro
115         120         125

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Gly	Arg	Ala	Leu	Leu	Val	Trp	Thr	Gly	Pro	Gly	Ala	Gly	Ser	Val	Thr
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145					150					155					160
Ala	Glu	Leu	Gly	Asp	Pro	Ala	Ser	Leu	Cys	Ala	Gly	Glu	Pro	Thr	Ala
				165					170						175
Leu	Leu	Val	Leu	Ala	Ser	Gln	Ala	Val	Pro	Ala	Leu	Cys	Met	Trp	Leu
			180						185					190	
Gly	Leu	Ala	Lys	Leu	Gly	Cys	Pro	Thr	Ala	Trp	Ile	Asn	Pro	His	Gly
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Arg	Gly	Met	Pro	Leu	Ala	His	Ser	Val	Leu	Ser	Ser	Gly	Ala	Arg	Val
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Leu	Val	Val	Asp	Pro	Asp	Leu	Arg	Glu	Ser	Leu	Glu	Glu	Ile	Leu	Pro
225					230						235				240
Lys	Leu	Gln	Ala	Glu	Asn	Ile	Arg	Cys	Phe	Tyr	Leu	Ser	His	Thr	Ser
				245					250						255
Pro	Thr	Pro	Gly	Val	Gly	Ala	Leu	Gly	Ala	Ala	Leu	Asp	Ala	Ala	Pro
			260					265					270		
Ser	His	Pro	Val	Pro	Ala	Asp	Leu	Arg	Ala	Gly	Ile	Thr	Trp	Arg	Ser
		275					280						285		
Pro	Ala	Leu	Phe	Ile	Tyr	Thr	Ser	Gly	Thr	Thr	Gly	Leu	Pro	Lys	Pro
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Leu	Ser	Gly	Ala	Thr	Ala	Asp	Asp	Val	Val	Tyr	Thr	Val	Leu	Pro	Leu
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Tyr	His	Val	Met	Gly	Leu	Val	Val	Gly	Ile	Leu	Gly	Cys	Leu	Asp	Leu
			340					345					350		
Gly	Ala	Thr	Cys	Val	Leu	Ala	Pro	Lys	Phe	Ser	Thr	Ser	Cys	Phe	Trp
		355					360					365			
Asp	Asp	Cys	Arg	Gln	His	Gly	Val	Thr	Val	Ile	Leu	Tyr	Val	Gly	Glu
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His	Thr	Val	Arg	Leu	Ala	Met	Gly	Asn	Gly	Leu	Arg	Ala	Asp	Val	Trp
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Asn	Val	Ser	Thr	His	Glu	Val	Glu	Gly	Val	Leu	Ser	Gln	Val	Asp	Phe
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Lys	Val	Gly	Met	Ala	Ala	Val	Gln	Leu	Ala	Pro	Gly	Gln	Thr	Phe	Asp
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	645	650
Ile Val Val Asp Pro Leu Phe Val Leu Asp Asn Arg Ala Gln Ser Phe		655
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Arg Pro Leu Thr Ala Glu Met Tyr Gln Ala Val Cys Glu Gly Thr Trp		670
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Arg Leu		685
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<210> 15
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 <212> DNA
 <213> Homosapien

<400> 15
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<210> 16
 <211> 368
 <212> PRT
 <213> Homosapien

<400> 16
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 20 25 30
 Val Gly Asn Gly Leu Val Leu Ala Val Leu Leu Gln Pro Gly Pro Ser
 35 40 45
 Ala Trp Gln Glu Pro Gly Ser Thr Thr Asp Leu Phe Ile Leu Asn Leu
 50 55 60
 Ala Val Ala Asp Leu Cys Phe Ile Leu Cys Cys Val Pro Phe Gln Ala
 65 70 75 80
 Thr Ile Tyr Thr Leu Asp Ala Trp Leu Phe Gly Ala Leu Val Cys Lys
 85 90 95
 Ala Val His Leu Leu Ile Tyr Leu Thr Met Tyr Ala Ser Ser Phe Thr
 100 105 110
 Leu Ala Ala Val Ser Val Asp Arg Tyr Leu Ala Val Arg His Pro Leu

115	120	125
Arg Ser Arg Ala Leu Arg Thr Pro Arg Asn Ala Arg Ala Ala Val Gly		
130	135	140
Leu Val Trp Leu Leu Ala Ala Leu Phe Ser Ala Pro Tyr Leu Ser Tyr		
145	150	155
Tyr Gly Thr Val Arg Tyr Gly Ala Leu Glu Leu Cys Val Pro Ala Trp		
165	170	175
Glu Asp Ala Arg Arg Arg Ala Leu Asp Val Ala Thr Phe Ala Ala Gly		
180	185	190
Tyr Leu Leu Pro Val Ala Val Val Ser Leu Ala Tyr Gly Arg Thr Leu		
195	200	205
Arg Phe Leu Trp Ala Ala Val Gly Pro Ala Gly Ala Ala Ala Ala Glu		
210	215	220
Ala Arg Arg Arg Ala Thr Gly Arg Ala Gly Arg Ala Met Leu Ala Val		
225	230	235
Ala Ala Leu Tyr Ala Leu Cys Trp Gly Pro His His Ala Leu Ile Leu		
245	250	255
Cys Phe Trp Tyr Gly Arg Phe Ala Phe Ser Pro Ala Thr Tyr Ala Cys		
260	265	270
Arg Leu Ala Ser His Cys Leu Ala Tyr Ala Asn Ser Cys Leu Asn Pro		
275	280	285
Leu Val Tyr Ala Leu Ala Ser Arg His Phe Arg Ala Arg Phe Arg Arg		
290	295	300
Leu Trp Pro Cys Gly Arg Arg Arg Arg His Arg Ala Arg Arg Ala Leu		
305	310	315
Arg Arg Val Arg Pro Ala Ser Ser Gly Pro Pro Gly Cys Pro Gly Asp		
325	330	335
Ala Arg Pro Ser Gly Arg Leu Leu Ala Gly Gly Gly Gln Gly Pro Glu		
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Pro Arg Glu Gly Pro Val His Gly Gly Glu Ala Ala Arg Gly Pro Glu		
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<210> 17

<211> 3763

<212> DNA

<213> Homosapien

<400> 17

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<210> 18

<211> 644

<212> PRT

<213> Homosapien

<400> 18

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20          25          30
Val Ala Leu Leu Leu Trp Ser Leu Ser Ser Leu Arg Glu Gln Lys Glu
35          40          45
Leu Asp Leu Met Asp Leu Val Gly Glu Asp Arg Lys Trp Met Met Ala
50          55          60
Arg Lys Leu Met Gln Val Asn Asp Thr Leu Thr Ser Glu Asp Ala Gly
65          70          75          80
Leu Arg Asn Ser Lys Asn Cys Thr Glu Pro Ala Leu His Glu Phe Pro
85          90          95
Asn Asp Ile Phe Thr Asn Glu Asp Arg Arg Gln Gly Ala Val Val Leu

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	100		105		110
His Val	Leu Cys Ala Ile Tyr Met	Phe Tyr Ala Leu Ala Ile Val Cys			
	115	120	125		
Asp Asp	Phe Phe Val Pro Ser Leu	Glu Lys Ile Cys Glu Arg Leu His			
	130	135	140		
Leu Ser	Glu Asp Val Ala Gly Ala Thr Phe Met Ala Ala Gly Ser Ser				
145	150	155	160		
Ala Pro	Glu Leu Phe Thr Ser Val Ile Gly Val Phe Ile Thr Lys Gly				
	165	170	175		
Asp Val	Gly Val Gly Thr Ile Val Gly Ser Ala Val Phe Asn Ile Leu				
	180	185	190		
Cys Ile	Ile Gly Val Cys Gly Leu Phe Ala Gly Gln Val Val Ala Leu				
	195	200	205		
Ser Ser	Trp Cys Leu Leu Arg Asp Ser Ile Tyr Tyr Thr Leu Ser Val				
	210	215	220		
Ile Ala	Leu Ile Val Phe Ile Tyr Asp Glu Lys Val Ser Trp Trp Glu				
225	230	235	240		
Ser Leu	Val Leu Val Leu Met Tyr Leu Ile Tyr Ile Val Ile Met Lys				
	245	250	255		
Tyr Asn	Ala Cys Ile His Gln Cys Phe Glu Arg Arg Thr Lys Gly Ala				
	260	265	270		
Gly Asn	Met Val Asn Gly Leu Ala Asn Asn Ala Glu Ile Asp Asp Ser				
	275	280	285		
Ser Asn	Cys Asp Ala Thr Val Val Leu Leu Lys Lys Ala Asn Phe His				
	290	295	300		
Arg Lys	Ala Ser Val Ile Met Val Asp Glu Leu Leu Ser Ala Tyr Pro				
305	310	315	320		
His Gln	Leu Ser Phe Ser Glu Ala Gly Leu Arg Ile Met Ile Thr Ser				
	325	330	335		
His Phe	Pro Pro Lys Thr Arg Leu Ser Met Ala Ser Arg Met Leu Ile				
	340	345	350		
Asn Glu	Arg Gln Arg Leu Ile Asn Ser Arg Ala Tyr Thr Asn Gly Glu				
	355	360	365		
Ser Glu	Val Ala Ile Lys Ile Pro Ile Lys His Thr Val Glu Asn Gly				
	370	375	380		
Thr Gly	Pro Ser Ser Ala Pro Asp Arg Gly Val Asn Gly Thr Arg Arg				
385	390	395	400		
Asp Asp	Val Val Ala Glu Ala Gly Asn Glu Thr Glu Asn Glu Asn Glu				
	405	410	415		
Asp Asn	Glu Asn Asp Glu Glu Glu Glu Asp Glu Asp Asp Asp Glu				
	420	425	430		
Gly Pro	Tyr Thr Pro Phe Asp Thr Pro Ser Gly Lys Leu Glu Thr Val				
	435	440	445		
Lys Trp	Ala Phe Thr Trp Pro Leu Ser Phe Val Leu Tyr Phe Thr Val				
	450	455	460		
Pro Asn	Cys Asn Lys Pro Arg Trp Glu Lys Trp Phe Met Val Thr Phe				
465	470	475	480		
Ala Ser	Ser Thr Leu Trp Ile Ala Ala Phe Ser Tyr Met Met Val Trp				
	485	490	495		
Met Val	Thr Ile Ile Gly Tyr Thr Leu Gly Ile Pro Asp Val Ile Met				
	500	505	510		
Gly Ile	Thr Phe Leu Ala Ala Gly Thr Ser Val Pro Asp Cys Met Ala				
	515	520	525		
Ser Leu	Ile Val Ala Arg Gln Gly Met Gly Asp Met Ala Val Ser Asn				
	530	535	540		
Ser Ile	Gly Ser Asn Val Phe Asp Ile Leu Ile Gly Leu Gly Leu Pro				
545	550	555	560		
Trp Ala	Leu Gln Thr Leu Ala Val Asp Tyr Gly Ser Tyr Ile Arg Leu				
	565	570	575		
Asn Ser	Arg Gly Leu Ile Tyr Ser Val Gly Leu Leu Leu Ala Ser Val				

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<210> 19
<211> 1228
<212> DNA
<213> Homosapien
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<220>
<221> misc_feature
<222> (1)...(1228)
<223> n = A,T,C or G
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<400> 19						
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cttctgcttt	aaaaagcttg	cggnaatttc	ttaataccga	cctcacctat	aggggaagtcg	180
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<210> 20
<211> 216
<212> PRT
<213> Homosapien
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<220>  
<221> VARIANT  
<222> (1)...(216)  
<223> Xaa = Any Amino Acid
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<400> 20															
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			20					25					30		
Glu	Val	Gly	Pro	His	Gly	Val	Arg	Pro	Ile	Leu	Tyr	Thr	Leu	Thr	Thr
		35					40					45			

Arg Pro Phe Ile Ile Ile Val Phe Ser Tyr Gly Ser Met Phe Tyr Ser

50	55	60
Val His Gln Ser Ala Ile Thr Ala Thr Glu Ile Arg Asn Gln Val Lys		
65	70	75
Lys Glu Met Ile Leu Ala Lys Arg Phe Phe Ile Val Phe Thr Asp		80
	85	90
Ala Leu Cys Trp Ile Pro Ile Phe Val Val Lys Phe Leu Ser Leu Leu		95
	100	105
Gln Val Glu Ile Pro Gly Thr Ile Thr Ser Trp Val Val Ile Phe Ile		110
	115	120
Leu Pro Ile Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr		125
	130	135
Arg Pro Phe Lys Glu Met Ile His Arg Phe Trp Tyr Asn Tyr Arg Gln		140
145	150	155
Arg Lys Ser Met Asp Ser Lys Gly Gln Lys Thr Tyr Ala Pro Ser Phe		160
	165	170
Ile Trp Val Glu Met Trp Pro Leu Gln Glu Met Pro Pro Glu Leu Met		175
	180	185
Lys Pro Asp Leu Phe Thr Tyr Pro Cys Glu Met Ser Leu Ile Ser Gln		190
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Ser Thr Arg Leu Asn Ser Tyr Ser		205
210	215	

<210> 21

<211> 3371

<212> DNA

<213> Homosapien

<400> 21

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<210> 22

<211> 739

<212> PRT

<213> Homosapien

<400> 22

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Lys Lys Asp Arg Asp Ser Cys Gly Arg Lys Asn Ser Glu Pro Gly Ser
          20          25          30
Pro His Ser Leu Glu Ala Leu Arg Asp Ala Ala Pro Ser Gln Gly Leu
          35          40          45
Asn Phe Leu Leu Leu Phe Thr Lys Met Leu Phe Ile Phe Asn Phe Leu
          50          55          60
Phe Ser Pro Leu Pro Thr Pro Ala Leu Ile Cys Ile Leu Thr Phe Gly
          65          70          75          80
Ala Ala Ile Phe Leu Trp Leu Ile Thr Arg Pro Gln Pro Val Leu Pro
          85          90          95
Leu Leu Asp Leu Asn Asn Gln Ser Val Gly Ile Glu Gly Gly Ala Arg
          100          105          110
Lys Gly Val Ser Gln Lys Asn Asn Asp Leu Thr Ser Cys Cys Phe Ser
          115          120          125
Asp Ala Lys Thr Met Tyr Glu Val Phe Gln Arg Gly Leu Ala Val Ser
          130          135          140
Asp Asn Gly Pro Cys Leu Gly Tyr Arg Lys Pro Asn Gln Pro Tyr Arg
          145          150          155          160
Trp Leu Ser Tyr Lys Gln Val Ser Asp Arg Ala Glu Tyr Leu Gly Ser
          165          170          175
Cys Leu Leu His Lys Gly Tyr Lys Ser Ser Pro Asp Gln Phe Val Gly
          180          185          190
Ile Phe Ala Gln Asn Arg Pro Glu Trp Ile Ile Ser Glu Leu Ala Cys
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Tyr Thr Tyr Ser Met Val Ala Val Pro Leu Tyr Asp Thr Leu Gly Pro

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210	215	220
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Cys Asp Thr Pro Gln	Lys Ala Leu Val Leu Ile Gly Asn Val Glu Lys	240
245	250	255
Gly Phe Thr Pro Ser	Leu Lys Val Ile Ile Leu Met Asp Pro Phe Asp	260
260	265	270
Asp Asp Leu Lys Gln	Arg Gly Glu Lys Ser Gly Ile Glu Ile Leu Ser	275
275	280	285
Leu Tyr Asp Ala Glu	Asn Leu Gly Lys Glu His Phe Arg Lys Pro Val	290
290	295	300
Pro Pro Ser Pro Glu	Asp Leu Ser Val Ile Cys Phe Thr Ser Gly Thr	305
305	310	315
Thr Gly Asp Pro Lys	Gly Ala Met Ile Thr His Gln Asn Ile Val Ser	320
325	330	335
Asn Ala Ala Ala Phe	Leu Lys Cys Val Glu His Ala Tyr Glu Pro Thr	340
340	345	350
Pro Asp Asp Val Ala	Ile Ser Tyr Leu Pro Leu Ala His Met Phe Glu	355
355	360	365
Arg Ile Val Gln Ala	Val Val Tyr Ser Cys Gly Ala Arg Val Gly Phe	370
370	375	380
Phe Gln Gly Asp Ile	Arg Leu Leu Ala Asp Asp Met Lys Thr Leu Lys	385
385	390	395
Pro Thr Leu Phe Pro	Ala Val Pro Arg Leu Leu Asn Arg Ile Tyr Asp	400
405	410	415
Lys Val Gln Asn Glu	Ala Lys Thr Pro Leu Lys Lys Phe Leu Leu Lys	420
420	425	430
Leu Ala Val Ser Ser	Lys Phe Lys Glu Leu Gln Lys Gly Ile Ile Arg	435
435	440	445
His Asp Ser Phe Trp	Asp Lys Leu Ile Phe Ala Lys Ile Gln Asp Ser	450
450	455	460
Leu Gly Gly Arg Val	Arg Val Ile Val Thr Gly Ala Ala Pro Met Ser	465
465	470	475
Thr Ser Val Met Thr	Phe Phe Arg Ala Ala Met Gly Cys Gln Val Tyr	480
485	490	495
Glu Ala Tyr Gly Gln	Thr Glu Cys Thr Gly Gly Cys Thr Phe Thr Leu	500
500	505	510
Pro Gly Asp Trp Thr	Ser Gly His Val Gly Val Pro Leu Ala Cys Asn	515
515	520	525
Tyr Val Lys Leu Glu	Asp Val Ala Asp Met Asn Tyr Phe Thr Val Asn	530
530	535	540
Asn Glu Gly Glu Val	Cys Ile Lys Gly Thr Asn Val Phe Lys Gly Tyr	545
545	550	555
Leu Lys Asp Pro Glu	Lys Thr Gln Glu Ala Leu Asp Ser Asp Gly Trp	560
565	570	575
Leu His Thr Gly Asp	Ile Gly Arg Trp Leu Pro Asn Gly Thr Leu Lys	580
580	585	590
Ile Ile Asp Arg Lys	Lys Asn Ile Phe Lys Leu Ala Gln Gly Glu Tyr	595
595	600	605
Ile Ala Pro Glu Lys	Ile Glu Asn Ile Tyr Asn Arg Ser Gln Pro Val	610
610	615	620
Leu Gln Ile Phe Val	His Gly Glu Ser Leu Arg Ser Ser Leu Val Gly	625
625	630	635
Val Val Val Pro Asp	Thr Asp Val Leu Pro Ser Phe Ala Ala Lys Leu	640
645	650	655
Gly Val Lys Gly Ser	Phe Glu Glu Leu Cys Gln Asn Gln Val Val Arg	660
660	665	670
Glu Ala Ile Leu Glu	Asp Leu Gln Lys Ile Gly Lys Glu Ser Gly Leu	675
675	680	685
Lys Thr Phe Glu Gln	Val Lys Ala Ile Phe Leu His Pro Glu Pro Phe	

690 695 700
 Ser Ile Glu Asn Gly Leu Leu Thr Pro Thr Leu Lys Ala Lys Arg Gly
 705 710 715 720
 Glu Leu Ser Lys Tyr Phe Arg Thr Gln Ile Asp Ser Leu Tyr Glu His
 725 730 735
 Ile Gln Asp

<210> 23
 <211> 1734
 <212> DNA
 <213> Homosapien

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<210> 24
 <211> 382
 <212> PRT
 <213> Homosapien

<400> 24
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 20 25 30
 Val Val Val Val Ala Leu Gly Leu Thr Val Ser Val Leu Val Leu Leu
 35 40 45
 Thr Asn Leu Leu Val Ile Ala Ala Ile Ala Ser Asn Arg Arg Phe His
 50 55 60
 Gln Pro Ile Tyr Tyr Leu Leu Gly Asn Leu Ala Ala Ala Asp Leu Phe

65					70					75				80	
Ala	Gly	Val	Ala	Tyr	Leu	Phe	Leu	Met	Phe	His	Thr	Gly	Pro	Arg	Thr
				85					90					95	
Ala	Arg	Leu	Ser	Leu	Glu	Gly	Trp	Phe	Leu	Arg	Gln	Gly	Leu	Leu	Asp
			100					105					110		
Thr	Ser	Leu	Thr	Ala	Ser	Val	Ala	Thr	Leu	Leu	Ala	Ile	Ala	Val	Glu
		115					120					125			
Arg	His	Arg	Ser	Val	Met	Ala	Val	Gln	Leu	His	Ser	Arg	Leu	Pro	Arg
	130					135					140				
Gly	Arg	Val	Val	Met	Leu	Ile	Val	Gly	Val	Trp	Val	Ala	Ala	Leu	Gly
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Leu	Gly	Leu	Leu	Pro	Ala	His	Ser	Trp	His	Cys	Leu	Cys	Ala	Leu	Asp
				165				170					175		
Arg	Cys	Ser	Arg	Met	Ala	Pro	Leu	Leu	Ser	Arg	Ser	Tyr	Leu	Ala	Val
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Trp	Ala	Leu	Ser	Ser	Leu	Leu	Val	Phe	Leu	Leu	Met	Val	Ala	Val	Tyr
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Thr	Arg	Ile	Phe	Phe	Tyr	Val	Arg	Arg	Arg	Val	Gln	Arg	Met	Ala	Glu
210					215						220				
His	Val	Ser	Cys	His	Pro	Arg	Tyr	Arg	Glu	Thr	Thr	Leu	Ser	Leu	Val
225					230				235					240	
Lys	Thr	Val	Val	Ile	Leu	Gly	Ala	Phe	Val	Val	Cys	Trp	Thr	Thr	Pro
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Val	Leu	Ala	Val	Glu	Lys	Tyr	Phe	Leu	Leu	Leu	Ala	Glu	Ala	Asn	Ser
	275						280					285			
Leu	Val	Asn	Ala	Ala	Val	Tyr	Ser	Cys	Arg	Asp	Ala	Glu	Met	Arg	Arg
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Thr	Phe	Arg	Arg	Leu	Leu	Cys	Cys	Ala	Cys	Leu	Arg	Gln	Ser	Thr	Arg
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Glu	Ser	Val	His	Tyr	Thr	Ser	Ser	Ala	Gln	Gly	Gly	Ala	Ser	Thr	Arg
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Ile	Met	Leu	Pro	Glu	Asn	Gly	His	Pro	Leu	Met	Thr	Pro	Pro	Phe	Ser
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Tyr	Leu	Glu	Leu	Gln	Arg	Tyr	Ala	Ala	Ser	Asn	Lys	Ser	Thr	Ala	Pro
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 <212> DNA
 <213> Homosapien

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<210> 26
 <211> 29
 <212> PRT
 <213> Homosapien

<400> 26
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Leu Arg Pro Lys Arg Ser Ser Leu Lys Ser Arg Ala Glu
20 25

<210> 27
<211> 3151
<212> DNA
<213> Homosapien

<400> 27

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<210> 28
 <211> 619
 <212> PRT
 <213> Homosapien

<400> 28
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 35 40 45
 Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
 50 55 60
 Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
 65 70 75 80
 Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys
 85 90 95
 Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
 100 105 110
 Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
 115 120 125
 Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
 130 135 140
 Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
 145 150 155 160
 Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
 165 170 175
 Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
 180 185 190
 Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
 195 200 205
 Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
 210 215 220
 Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
 225 230 235 240
 Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
 245 250 255
 Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
 260 265 270
 His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
 275 280 285
 Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
 290 295 300
 Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
 305 310 315 320
 Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn
 325 330 335
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 340 345 350
 Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile
 355 360 365
 Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met
 370 375 380
 Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg
 385 390 395 400
 Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met

27/136

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<210> 30

<211> 357

<212> PRT

<213> Homosapien

<400> 30

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          20          25          30
Asn Glu Val Leu Leu Arg Met His Ser Val Gly Ile Cys Gly Ser Asp
          35          40          45
Val His Tyr Trp Glu Tyr Gly Arg Ile Gly Asn Phe Ile Val Lys Lys
          50          55          60
Pro Met Val Leu Gly His Glu Ala Ser Gly Thr Val Glu Lys Val Gly
65          70          75          80
Ser Ser Val Lys His Leu Lys Pro Gly Asp Arg Val Ala Ile Glu Pro
          85          90          95
Gly Ala Pro Arg Glu Asn Asp Glu Phe Cys Lys Met Gly Arg Tyr Asn
          100          105          110
Leu Ser Pro Ser Ile Phe Phe Cys Ala Thr Pro Pro Asp Asp Gly Asn
          115          120          125
Leu Cys Arg Phe Tyr Lys His Asn Ala Ala Phe Cys Tyr Lys Leu Pro
          130          135          140
Asp Asn Val Thr Phe Glu Glu Gly Ala Leu Ile Glu Pro Leu Ser Val
145          150          155          160
Gly Ile His Ala Cys Arg Arg Gly Gly Val Thr Leu Gly His Lys Val
          165          170          175
Leu Val Cys Gly Ala Gly Pro Ile Gly Met Val Thr Leu Leu Val Ala
          180          185          190
Lys Ala Met Gly Ala Ala Gln Val Val Val Thr Asp Leu Ser Ala Thr
          195          200          205
Arg Leu Ser Lys Ala Lys Glu Ile Gly Ala Asp Leu Val Leu Gln Ile
          210          215          220
Ser Lys Glu Ser Pro Gln Glu Ile Ala Arg Lys Val Glu Gly Gln Leu
225          230          235          240
Gly Cys Lys Pro Glu Val Thr Ile Glu Cys Thr Gly Ala Glu Ala Ser
          245          250          255
Ile Gln Ala Gly Ile Tyr Ala Thr Arg Ser Gly Gly Thr Leu Val Leu
          260          265          270
Val Gly Leu Gly Ser Glu Met Thr Thr Val Pro Leu Leu His Ala Ala
          275          280          285
Ile Arg Glu Val Asp Ile Lys Gly Val Phe Arg Tyr Cys Asn Thr Trp
          290          295          300
Pro Val Ala Ile Ser Met Leu Ala Ser Lys Ser Val Asn Val Lys Pro
305          310          315          320
Leu Val Thr His Arg Phe Pro Leu Glu Lys Ala Leu Glu Ala Phe Glu
          325          330          335
Thr Phe Lys Lys Gly Leu Gly Leu Lys Ile Met Leu Lys Cys Asp Pro
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Ser Asp Gln Asn Pro
          355

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<210> 31

<211> 2682
 <212> DNA
 <213> Homosapien

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 Glu Asn Thr Arg Phe Arg Gly Trp Leu Val Arg Arg Leu Cys Tyr Phe
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<211> 697

<212> PRT

<213> Homosapien

<400> 34

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Glu Tyr Asp Lys Met Lys Arg Gly Ser Arg Lys Gly Ser Ile Glu Ile
65     70     75     80
Lys Lys Ile Arg Cys Val Glu Lys Val Asn Leu Glu Glu Gln Thr Pro
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Leu Gln Lys Glu Ile Arg Gly Asn Pro His Leu Leu Val Lys Tyr His
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Ser Gly Phe Phe Val Asp Gly Lys Phe Leu Cys Cys Gln Gln Ser Cys
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Thr Ala Val Asn Glu Glu Lys His Arg Val Pro Thr Phe Pro Asp Arg
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Val Leu Lys Ile Pro Arg Ala Val Pro Val Leu Lys Met Asp Ala Pro
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Tyr Gly Ser Gln Pro Pro Ser Ser Ser Thr Ser Leu Ala Gln Tyr Asp
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<211> 2080

<212> PRT

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 Ser Val Leu Ala Tyr Phe Pro Asn Trp Leu Phe Gln Gln Arg Glu Ser
 465 470 475 480
 Lys Met Lys Leu Pro Pro Ala Leu Glu Thr Pro Met Arg Ser Gln Glu
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 Ser Gln Pro Phe Leu Leu Lys Ser Val Pro Arg Arg Ser Leu Arg Ser
 500 505 510
 Pro Pro Gln Pro Ala Pro Ser Ala Ala Pro Pro Cys Gln Leu Ala Val
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 Phe Gln Ser Thr Trp Ile Arg Met Asp Glu Ala Ser Val Trp Thr Val
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 Gln Ile Ile Pro Gln Ser His Pro Val Asn Pro Leu Leu Thr Trp Leu
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 Gly Ser Asp Lys Ala Gln Lys Lys Arg Lys Ser Arg Gly Lys Ser Gln
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 Ser Pro Ser Leu Pro Val Leu Phe Pro Ser Ser Gln Glu Ile Cys Leu
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 Leu Phe Pro Leu Trp Glu Val Gln Cys Leu Pro Ile Pro Cys Pro Arg
 595 600 605
 Thr Leu Leu Leu His Glu Ile Pro Leu Pro Ala Glu Ile Pro Gln Gln
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 Leu Leu Pro Val His Ile Ser Arg Leu Ser Thr Val Arg Gly Arg Thr
 625 630 635 640
 Thr Ala Leu Pro Ser Glu Pro Ser Gly Cys Met Trp Glu Thr Val Thr
 645 650 655
 Ser Ile Gln Cys Thr Ile Ser Ser Gly Met Lys Lys Glu Val Arg His
 660 665 670
 Ala Arg Gln Asp Arg Leu Glu Ile Leu Ser Leu Thr Ser Met Glu Asn
 675 680 685
 Gln Cys Met Asp Leu Ser Thr Gln Lys Leu Asn Ser Tyr Arg Val Gly
 690 695 700
 Ile Arg Cys Gln Ser Leu Leu Pro His Leu Lys Thr His Gln Ser Lys
 705 710 715 720
 Leu Asp Gln Pro Gly Glu Thr Ala Ile Arg Ala Gly Trp Gly Gly Ala
 725 730 735
 Arg Asn Pro Arg Arg Lys Lys Val Ser Lys Gly Gly Asp Leu Phe Ser
 740 745 750
 Lys Ser Pro Ser Ser Leu Leu Leu Tyr Ser Thr Pro Ala Glu Val Ser
 755 760 765
 Pro Ala Thr Asp Pro Cys His Arg Val Arg Ala Ser Gln Val Pro Pro
 770 775 780
 Leu Ile Ala Cys Leu Pro Gly Leu Gln His Gln Ala Thr Ala Pro Pro
 785 790 795 800
 Leu Thr Ser His Leu Val Leu Ile Pro Pro Arg Ala Ala Pro Leu Val
 805 810 815
 Leu Val Pro Pro Ile Pro Gln Gln Gly Pro Gly Thr Ser Gly Pro Ala
 820 825 830
 Leu Ser Thr Val Leu His Pro Asn Ser Ala Gly Ser Gly Thr Gly Pro
 835 840 845
 Glu Gly Glu Ser Pro Pro Ala Thr Ser His Cys Pro Arg Trp Pro Gly
 850 855 860
 Arg Pro Leu Gln Pro Arg Asn Pro Pro Pro Arg Ser Gly His His Pro
 865 870 875 880
 Leu Phe Trp Asp Thr His Trp Ala Ile Pro Arg Ser Arg Lys Pro Phe
 885 890 895
 Pro Ala Arg Cys Thr Pro Arg Pro Pro Ser Ser Asp Thr Ser Gly Pro

	900		905		910
Arg Val	Arg Ser Pro Pro Gly	Pro Arg Cys Ser Ser	Ala Cys Ser Pro		
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	930	935	940		
Pro Ala	Ser Thr Ala Trp Arg	Pro Lys Arg Arg	Cys Ser Gly Ser Ser		
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Pro Ser	Gly Arg Arg Cys Arg	Ala Trp Met Arg	Thr Cys Ala Thr		
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Cys Arg	Arg Ser Ala Ala Pro	Gly Gln Trp Ser	Lys Ala Ala Asn Ala		
	980	985	990		
Gln Ser	Pro Gly Arg Trp Ala	Ala Arg Ser Leu	Trp Thr Thr Trp Thr		
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Ala Thr	Ser Arg Pro Arg Trp	Trp Arg Lys Gln	Thr Ala Ser Gln Arg		
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Thr Leu	Leu Cys Leu Ser Trp	Lys Arg Glu Arg	Arg Lys Ser Ile Arg		
	1045	1050	1055		
Arg Leu	Trp Lys Gly Gln Val	Leu Leu Lys Thr	Lys Arg Leu Cys Arg		
	1060	1065	1070		
Arg Arg	His Arg Trp Ala Ala	Cys Arg Met Leu	Phe Thr Ser Arg Pro		
	1075	1080	1085		
Ala Cys	Ala Pro Ala Arg Val	Arg Cys Arg Met	Ala Arg Cys Leu Arg		
	1090	1095	1100		
Ser Thr	Ala Arg Val Ala Gly	Thr Ser Asp Gly	Pro Pro Leu Leu Ala		
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Pro Ser	Arg Met Val Ser Ala	Thr Pro Ser Thr	Gly Ala Ser Leu Gly		
	1125	1130	1135		
Arg Gly	Lys Ala Arg Arg Ser	Pro Pro Arg Pro	Arg Ser Phe Ser Asp		
	1140	1145	1150		
Val Lys	Ser Thr Ala Ser Trp	Pro Thr Ser Ile	Thr Ser Glu Arg Lys		
	1155	1160	1165		
Cys His	Leu Arg Thr Lys Arg	Thr Thr Ser Ala	Leu Cys Ser Pro Arg		
	1170	1175	1180		
Gln Leu	Ala Pro Thr Asn Ala	Cys Gln Gly Thr	Gln Ser Asp Pro Arg		
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Val Gly	Ser Arg Ser Pro Arg	Arg Leu Leu Arg	Ala Glu Leu Leu Ser		
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Ala Ala	Pro Met Gln Leu Arg	Val Pro Ser Leu	Leu Phe Pro Ser Arg		
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Pro Gln	Ala Gly Trp Thr Val	Glu Arg Arg Ser	Leu Ala Trp Leu Leu		
	1235	1240	1245		
Leu Ser	Pro Leu Leu Gly Arg	Ala Pro Pro Ser	Ile Ser Trp Lys Val		
	1250	1255	1260		
Gly Leu	Ser His Ala Trp Ser	Arg Ser Arg Ala	Leu Trp Thr Leu Leu		
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Ser Cys	Pro Asp Leu Arg Pro	Pro Arg Gln Asn	Cys Leu Pro Gln Ser		
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Leu His	Arg Ala Pro Ala Gln	Val Val Thr Gly	Pro Leu Cys His Gln		
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Phe Ser	Pro Ala Ala Val Gly	Lys Arg Thr Ile	Pro Pro Val Gln Glu		
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Ser Phe	Leu Leu Pro Ala Arg	Ile Asn Pro Thr	Cys Trp Ser Leu Gly		
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Gly Ala	Leu Glu Gln Ser Trp	Lys Ala Ile Pro	Asn Arg Glu Arg Ala		
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 Trp Gly Arg Thr Ser Thr Ala Leu Thr Trp Pro Gly His Ala Ala Arg
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 Ser His Leu Lys Leu Pro Pro Gln Gly Arg Ser Gln Ala Gly Asn Arg
 1425 1430 1435 1440
 Leu Lys Glu Ala Leu Pro Gln Pro Glu Ala Ser Ala Leu Leu Arg Gly
 1445 1450 1455
 Leu Thr His Ala Glu Ser Pro Pro Trp Asn Cys Ala Phe Gln Lys Leu
 1460 1465 1470
 Arg Lys Pro Val Thr Thr Pro Lys Ile Ser Ser Leu Trp Glu Gly Pro
 1475 1480 1485
 Thr Gln Ile Ser Ile His Arg Pro Arg Pro Trp Arg Lys His Gly Arg
 1490 1495 1500
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 Arg Ser Trp Ala Arg Gly Val Ala Trp Asn Pro Ser Pro Lys Arg Phe
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 1620 1625 1630
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 Asn Gln Val Ser Gly Pro Gln Arg Ala Lys Ser Leu Pro Leu Ser Pro
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 Ser Val Ala Leu Ala Glu Arg Gly Arg Ala Thr Val Arg Val Gly Arg
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 Met Cys Phe Leu Leu Pro Gln Ala Pro Arg Thr Lys Pro Ala Met Gly
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 Cys Trp Arg Ser Leu Cys Ile Cys Gln Gly Arg Asp Thr Gln Gly Leu
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 Val Ser Gln Arg Thr Arg Asn Cys Pro Leu Leu Val Lys Ser Lys Pro
 1780 1785 1790
 Cys Leu Gln Ser Thr Pro Asn His Pro Leu Lys Ile Ala Pro Pro Cys
 1795 1800 1805
 Ala Asn Arg Gln Thr Thr Asp Arg Gln Thr Lys Ala Arg Val Ser Arg
 1810 1815 1820
 Pro Pro Thr Pro Thr Glu Gly Arg Lys Gly Arg Asn Ala Leu Lys His
 1825 1830 1835 1840
 Phe Met Leu Gln Gln Arg Ala Thr Ser Ser Arg Pro Ala Phe Pro Leu
 1845 1850 1855
 Cys Ile Ala Arg Thr Gly Lys Ala Arg Ser Gly Gln Pro Arg Gly Trp
 1860 1865 1870
 Gly Arg Ala Ser Leu Arg Pro Glu Gly Lys Gly Pro Val Pro Arg Ser

1875	1880	1885
His Arg Arg Arg Gln Thr Ser Pro Met Ala Asn Gly Pro Pro Gln Pro		
1890	1895	1900
Leu Gly Arg Val Leu Ser Asp Pro Arg Pro Ser Arg Lys Ser Leu Ala		
1905	1910	1915
Ala Pro Pro Ala Ser Leu Lys Pro Gly Pro Glu Leu Glu Arg Pro Leu		1920
	1925	1930
Gln Pro Ala Ala Thr Pro Leu Leu Pro Arg Pro Pro Gly Ala Cys Trp		1935
	1940	1945
Ser Phe Gln Pro Pro Ala Thr Gly Thr Ile Gly Arg Leu Ser Leu Pro		1950
	1955	1960
Gly Arg Ala Glu Pro Thr Gln Arg Val Thr Pro Cys Pro Pro Ser Gly		1965
	1970	1975
Ser Pro Pro Cys Leu Trp Ser His Thr Thr Pro Thr Gln Thr Pro Trp		1980
1985	1990	1995
Ala Gly Pro Ala Thr Gly Thr Gly Leu Ser Arg Leu Pro Pro Gly Lys		2000
	2005	2010
Pro Lys Gly Arg Thr Leu Pro Gln Pro Ser Leu Pro Gln Leu Gly Asn		2015
	2020	2025
Arg Thr Trp Ala Glu Thr Pro Ser His Pro Gln Pro Gln Thr Leu Thr		2030
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Ala Pro Ser Leu Phe Leu Met Arg Arg Thr Leu Trp Tyr Gly Arg Gly		2045
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2065	2070	2075
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 <212> DNA
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<211> 577

<212> PRT

<213> Homosapien

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          35          40          45
Phe Asn Phe Ala Ser Tyr Val Leu Asp Tyr Trp Ala Gln Lys Glu Lys
          50          55          60
Glu Gly Lys Arg Gly Pro Asn Pro Ala Phe Trp Trp Val Asn Gly Gln
          65          70          75          80
Gly Asp Glu Val Lys Trp Ser Phe Arg Glu Met Gly Asp Leu Thr Arg
          85          90          95
Arg Val Ala Asn Val Phe Thr Gln Thr Cys Gly Leu Gln Gln Gly Asp
          100          105          110
His Leu Ala Leu Met Leu Pro Arg Val Pro Glu Trp Trp Leu Val Ala
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Leu Lys Ala Lys Asp Ile Leu Tyr Arg Leu Gln Leu Ser Lys Ala Lys
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Gly Ile Val Thr Ile Asp Ala Leu Ala Ser Glu Val Asp Ser Ile Ala
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Ser Gln Cys Pro Ser Leu Lys Thr Lys Leu Leu Val Ser Asp His Ser
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Arg Glu Gly Trp Leu Asp Phe Arg Ser Leu Val Lys Ser Ala Ser Pro
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Val Ala Thr Ile Trp Thr Leu Val Glu Pro Trp Thr Ala Gly Cys Thr
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Val Phe Ile His His Leu Pro Gln Phe Asp Thr Lys Val Ile Ile Gln
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Thr Leu Leu Lys Tyr Pro Ile Asn His Phe Trp Gly Val Ser Ser Ile
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Tyr Arg Met Ile Leu Gln Gln Asp Phe Thr Ser Ile Arg Phe Pro Ala
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Leu Glu His Cys Tyr Thr Gly Gly Glu Val Val Leu Pro Lys Asp Gln
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Glu Glu Trp Lys Arg Arg Thr Gly Leu Leu Leu Tyr Glu Asn Tyr Gly
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Gln Ser Glu Thr Gly Leu Ile Cys Ala Thr Tyr Trp Gly Met Lys Ile
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Glu Gly Asp Pro Glu Lys Thr Ala Lys Val Glu Cys Gly Asp Phe Tyr						
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Asn Thr Gly Asp Arg Gly Lys Met Asp Glu Glu Gly Tyr Ile Cys Phe						
	450			455		460
Leu Gly Arg Ser Asp Asp Ile Ile Asn Ala Ser Gly Tyr Arg Ile Gly						
	465			470		475
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Ser Ala Val Val Gly Ser Pro Asp Pro Ile Arg Gly Glu Val Val Lys						
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Ala Phe Ile Val Leu Thr Pro Gln Phe Leu Ser His Asp Lys Asp Gln						
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Leu Thr Lys Glu Leu Gln Gln His Val Lys Ser Val Thr Ala Pro Tyr						
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Lys Tyr Pro Arg Asn Val Glu Phe Val Ser Glu Leu Pro Lys Thr Ile						
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Met						

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<210> 40

<211> 1037

<212> PRT

<213> Homosapien

<400> 40

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          20           25           30
Ser Ala Pro Arg Arg Ala Pro Leu Trp Thr Cys Leu Leu Leu Cys Ala
          35           40           45
Ala Leu Arg Thr Leu Leu Ala Ser Pro Ser Asn Glu Val Asn Leu Leu
          50           55           60
Asp Ser Arg Thr Val Met Gly Asp Leu Gly Trp Ile Ala Phe Pro Lys
          65           70           75           80
Asn Gly Trp Glu Glu Ile Gly Glu Val Asp Glu Asn Tyr Ala Pro Ile
          85           90           95
His Thr Tyr Gln Val Cys Lys Val Met Glu Gln Asn Gln Asn Asn Trp
          100          105          110
Leu Leu Thr Ser Trp Ile Ser Asn Glu Gly Ala Ser Arg Ile Phe Ile
          115          120          125

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Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Gly Leu
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 Gly Thr Cys Lys Glu Thr Phe Asn Met Tyr Tyr Phe Glu Ser Asp Asp
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 Gln Asn Gly Arg Asn Ile Lys Glu Asn Gln Tyr Ile Lys Ile Asp Thr
 165 170 175
 Ile Ala Ala Asp Glu Ser Phe Thr Glu Leu Asp Leu Gly Asp Arg Val
 180 185 190
 Met Lys Leu Asn Thr Glu Val Arg Asp Val Gly Pro Leu Ser Lys Lys
 195 200 205
 Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val
 210 215 220
 Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Ser Val Val Arg His Leu
 225 230 235 240
 Ala Val Phe Pro Asp Thr Ile Thr Gly Ala Asp Ser Ser Gln Leu Leu
 245 250 255
 Glu Val Ser Gly Ser Cys Val Asn His Ser Val Thr Asp Glu Pro Pro
 260 265 270
 Lys Met His Cys Ser Ala Glu Gly Glu Trp Leu Val Pro Ile Gly Lys
 275 280 285
 Cys Met Cys Lys Ala Gly Tyr Glu Glu Lys Asn Gly Thr Cys Gln Val
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 Cys Arg Pro Gly Phe Phe Lys Ala Ser Pro His Ile Gln Ser Cys Gly
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 Lys Cys Pro Pro His Ser Tyr Thr His Glu Glu Ala Ser Thr Ser Cys
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 Val Cys Glu Lys Asp Tyr Phe Arg Arg Glu Ser Asp Pro Pro Thr Met
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 Ala Cys Thr Arg Pro Pro Ser Ala Pro Arg Asn Ala Ile Ser Asn Val
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 465 470 475 480
 Ala Lys Asn Ser Ile Ser Leu Ser Trp Gln Glu Pro Asp Arg Pro Asn
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 Gly Ile Ile Leu Glu Tyr Glu Ile Lys His Phe Glu Lys Asp Gln Glu
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 Thr Ser Tyr Thr Ile Ile Lys Ser Lys Glu Thr Thr Ile Thr Ala Glu
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 Gly Leu Lys Pro Ala Ser Val Tyr Val Phe Gln Ile Arg Ala Arg Thr
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 Val Ser Val Thr Val Gly Val Ile Leu Leu Ala Val Val Ile Gly Val
 580 585 590
 Leu Leu Ser Gly Ser Cys Cys Glu Cys Gly Cys Gly Arg Ala Ser Ser
 595 600 605
 Leu Cys Ala Val Ala His Pro Ile Leu Ile Trp Arg Cys Gly Tyr Ser

610	615	620
Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His Asn Gly		
625	630	635
His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His Thr Tyr		
	645	650
Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile Glu Ala		
	660	665
Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe Gly Glu		
	675	680
Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu Pro Val		
	690	695
Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg Arg Asp		
705	710	715
Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro Asn Ile		
	725	730
Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met Ile Val		
	740	745
Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys Lys Asn		
	755	760
Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg Gly Ile		
	770	775
Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His Arg Asp		
785	790	795
Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys Lys Val		
	805	810
Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala		
	820	825
Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu		
	835	840
Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr		
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Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro Tyr Trp		
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Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly Tyr Arg		
	885	890
Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu		
	900	905
Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp Glu Ile		
	915	920
Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu Lys Thr		
	930	935
Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu His Ser		
945	950	955
Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu Glu Ala		
	965	970
Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly Tyr Ser		
	980	985
Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg Arg Leu		
	995	1000
Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser Leu Gln		
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<210> 41
 <211> 2180
 <212> DNA
 <213> Homosapien

<400> 41

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<210> 42
 <211> 517
 <212> PRT
 <213> Homosapien

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<400> 42
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          20          25          30
Pro Leu Ala Gln Phe Arg Glu Asp Ile Thr Trp Arg Arg Pro Gln Glu
          35          40          45
Ile Cys Ala Thr Pro Arg Leu Phe Pro Asp Asp Pro Arg Glu Gly Gln
          50          55          60
Val Lys Gln Gly Leu Leu Gly Asp Cys Trp Phe Leu Cys Ala Cys Ala
          65          70          75          80
Ala Leu Gln Lys Ser Arg His Leu Leu Asp Gln Val Ile Pro Pro Gly
          85          90          95
Gln Pro Ser Trp Ala Asp Gln Glu Tyr Arg Gly Ser Phe Thr Cys Arg
          100         105         110
Ile Trp Gln Phe Gly Arg Trp Val Glu Val Thr Thr Asp Asp Arg Leu

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115	120	125
Pro Cys Leu Ala Gly Arg Leu Cys Phe Ser Arg Cys Gln Arg Glu Asp		
130	135	140
Val Phe Trp Leu Pro Leu Leu Glu Lys Val Tyr Ala Lys Val His Gly		
145	150	155
Ser Tyr Glu His Leu Trp Ala Gly Gln Val Ala Asp Ala Leu Val Asp		
165	170	175
Leu Thr Gly Gly Leu Ala Glu Arg Trp Asn Leu Lys Gly Val Ala Gly		
180	185	190
Ser Gly Gly Gln Gln Asp Arg Pro Gly Arg Trp Glu His Arg Thr Cys		
195	200	205
Arg Gln Leu Leu His Leu Lys Asp Gln Cys Leu Ile Ser Cys Cys Val		
210	215	220
Leu Ser Pro Arg Ala Gly Ala Arg Glu Leu Gly Glu Phe His Ala Phe		
225	230	235
Ile Val Ser Asp Leu Arg Glu Leu Gln Gly Gln Ala Gly Gln Cys Ile		
245	250	255
Leu Leu Leu Arg Ile Gln Asn Pro Trp Gly Arg Arg Cys Trp Gln Gly		
260	265	270
Leu Trp Arg Glu Gly Gly Glu Gly Trp Ser Gln Val Asp Ala Ala Val		
275	280	285
Ala Ser Glu Leu Leu Ser Gln Leu Gln Glu Gly Glu Phe Trp Val Glu		
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Glu Glu Glu Phe Leu Arg Glu Phe Asp Glu Leu Thr Val Gly Tyr Pro		
305	310	315
Val Thr Glu Ala Gly His Leu Gln Ser Leu Tyr Thr Glu Arg Leu Leu		
325	330	335
Cys His Thr Arg Ala Leu Pro Gly Ala Trp Val Lys Gly Gln Ser Ala		
340	345	350
Gly Gly Cys Arg Asn Asn Ser Gly Phe Pro Ser Asn Pro Lys Phe Trp		
355	360	365
Leu Arg Val Ser Glu Pro Ser Glu Val Tyr Ile Ala Val Leu Gln Arg		
370	375	380
Ser Arg Leu His Ala Ala Asp Trp Ala Gly Arg Ala Arg Ala Leu Val		
385	390	395
Gly Asp Ser His Thr Ser Trp Ser Pro Ala Ser Ile Pro Gly Lys His		
405	410	415
Tyr Gln Ala Val Gly Leu His Leu Trp Lys Val Pro Glu Gly Gly Arg		
420	425	430
Ser Gln Asp Ala Pro Pro Leu Leu Leu Gln Glu Pro Leu Leu Ser Cys		
435	440	445
Val Pro His Arg Tyr Ala Gln Glu Val Ser Arg Leu Cys Leu Leu Pro		
450	455	460
Ala Gly Thr Tyr Lys Val Val Pro Ser Thr Tyr Leu Pro Asp Thr Glu		
465	470	475
Gly Ala Phe Thr Val Thr Ile Ala Thr Arg Ile Asp Arg Pro Ser Ile		
485	490	495
His Ser Gln Glu Met Leu Gly Gln Phe Leu Gln Glu Val Ser Val Met		
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Ala Val Met Lys Thr		
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<210> 43

<211> 1676

<212> DNA

<213> Homosapien

<400> 43

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<210> 44

<211> 352

<212> PRT

<213> Homosapien

<400> 44

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20          25          30
Arg Val Thr Pro Thr Cys His Ser Ser Thr Ser Glu Pro Arg Cys Ser
35          40          45
Arg Phe Asp Pro Asp Gly Ser Gly Ser Pro Ala Thr Trp Asp Asn Phe
50          55          60
Gly Ile Trp Asp Asn Arg Ile Asp Glu Pro Ile Leu Leu Pro Pro Ser
65          70          75          80
Ile Lys Tyr Gly Lys Pro Ile Pro Lys Ile Ser Leu Glu Asn Val Gly
85          90          95
Cys Ala Ser Gln Ile Gly Lys Arg Lys Glu Asn Glu Asp Arg Phe Asp
100          105          110
Phe Ala Gln Leu Thr Asp Glu Val Leu Tyr Phe Ala Val Tyr Asp Gly
115          120          125
His Gly Gly Pro Ala Ala Ala Asp Phe Cys His Thr His Met Glu Lys
130          135          140
Cys Ile Met Asp Leu Leu Pro Lys Glu Lys Asn Leu Glu Thr Leu Leu
145          150          155          160
Thr Leu Ala Phe Leu Glu Ile Asp Lys Ala Phe Ser Ser His Ala Arg
165          170          175
Leu Ser Ala Asp Ala Thr Leu Leu Thr Ser Gly Thr Thr Ala Thr Val
180          185          190
Ala Leu Leu Arg Asp Gly Ile Glu Leu Val Val Ala Ser Val Gly Asp
195          200          205
Ser Arg Ala Ile Leu Cys Arg Lys Gly Lys Pro Met Lys Leu Thr Ile
210          215          220

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Asp	His	Thr	Pro	Glu	Arg	Lys	Asp	Glu	Lys	Glu	Arg	Ile	Lys	Lys	Cys
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Gly	Gly	Phe	Val	Ala	Trp	Asn	Ser	Leu	Gly	Gln	Pro	His	Val	Asn	Gly
				245					250					255	
Arg	Leu	Ala	Met	Thr	Arg	Ser	Ile	Gly	Asp	Leu	Asp	Leu	Lys	Thr	Ser
			260					265					270		
Gly	Val	Ile	Ala	Glu	Pro	Glu	Thr	Lys	Arg	Ile	Lys	Leu	His	His	Ala
		275					280					285			
Asp	Asp	Ser	Phe	Leu	Val	Leu	Thr	Thr	Asp	Gly	Ile	Asn	Phe	Met	Val
	290					295					300				
Asn	Ser	Gln	Glu	Ile	Cys	Asp	Phe	Val	Asn	Gln	Cys	His	Asp	Pro	Asn
305					310					315					320
Glu	Ala	Ala	His	Ala	Val	Thr	Glu	Gln	Val	Thr	Gln	Ser	Phe	Cys	Leu
			325					330						335	
Lys	Ser	Pro	Lys	Glu	Lys	Glu	Gly	Lys	Asp	Ser	Pro	Gly	Ile	Val	Phe
			340					345					350		

<210> 45
 <211> 1680
 <212> DNA
 <213> Homosapien

<400> 45
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 aatggatcca ttagttctca taccatgaag aaattaatag cccagaagcc agatcttaaa 480
 atccacgatc agatgactgt gattgacaag ggaaagaaaa gaactttgga agaattgttc 540
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 aaagatgtca taaaagaatt tgcagatgac ggcgtcaagt acctggaact aaggagcaca 660
 cccagaagag aaaatgctac tggaaatgact aaaaagactt atgtggaatc tatacttgaa 720
 ggtataaaac agtccaaaca agaaaacttg gacattgatg ttaggtattt gatagcagtt 780
 gacagaagag gtggcccttt agtagccaag gagactgtaa aacttgccga ggagttcttc 840
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 gcaaaagact tcttggaaacc tcttttagaa gctaagaaag caggtctgaa gttagcattg 960
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 gactttgtga ggcaacatcg gataccactg gaactctgtt tgacctcaa cgtcaaaagt 1140
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 atacgtgtct tcaactgact cacaagctct caggtgctta ctgggtggga cttgactgtt 1620
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<210> 46
 <211> 355
 <212> PRT
 <213> Homosapien

<400> 46
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		20						25					30		
Ser	His	Thr	Met	Lys	Lys	Leu	Ile	Ala	Gln	Lys	Pro	Asp	Leu	Lys	Ile
		35						40				45			
His	Asp	Gln	Met	Thr	Val	Ile	Asp	Lys	Gly	Lys	Lys	Arg	Thr	Leu	Glu
		50					55				60				
Glu	Cys	Phe	Gln	Met	Phe	Gln	Thr	Ile	His	Gln	Leu	Thr	Ser	Ser	Pro
65					70					75					80
Glu	Asp	Ile	Leu	Met	Val	Thr	Lys	Asp	Val	Ile	Lys	Glu	Phe	Ala	Asp
				85					90					95	
Asp	Gly	Val	Lys	Tyr	Leu	Glu	Leu	Arg	Ser	Thr	Pro	Arg	Arg	Glu	Asn
		100						105					110		
Ala	Thr	Gly	Met	Thr	Lys	Lys	Thr	Tyr	Val	Glu	Ser	Ile	Leu	Glu	Gly
		115						120					125		
Ile	Lys	Gln	Ser	Lys	Gln	Glu	Asn	Leu	Asp	Ile	Asp	Val	Arg	Tyr	Leu
		130				135					140				
Ile	Ala	Val	Asp	Arg	Arg	Gly	Gly	Pro	Leu	Val	Ala	Lys	Glu	Thr	Val
145					150					155					160
Lys	Leu	Ala	Glu	Glu	Phe	Phe	Leu	Ser	Thr	Glu	Gly	Thr	Val	Leu	Gly
				165					170					175	
Leu	Asp	Leu	Ser	Gly	Asp	Pro	Thr	Val	Gly	Gln	Ala	Lys	Asp	Phe	Leu
		180						185					190		
Glu	Pro	Leu	Leu	Glu	Ala	Lys	Lys	Ala	Gly	Leu	Lys	Leu	Ala	Leu	His
		195					200					205			
Leu	Ser	Glu	Ile	Pro	Asn	Gln	Lys	Lys	Glu	Thr	Gln	Ile	Leu	Leu	Asp
		210				215					220				
Leu	Leu	Pro	Asp	Arg	Ile	Gly	His	Gly	Thr	Phe	Leu	Asn	Ser	Gly	Glu
225					230					235					240
Gly	Gly	Ser	Leu	Asp	Leu	Val	Asp	Phe	Val	Arg	Gln	His	Arg	Ile	Pro
				245					250					255	
Leu	Glu	Leu	Cys	Leu	Thr	Ser	Asn	Val	Lys	Ser	Gln	Thr	Val	Pro	Ser
		260						265					270		
Tyr	Asp	Gln	His	His	Phe	Gly	Phe	Trp	Tyr	Ser	Ile	Ala	His	Pro	Ser
		275					280					285			
Val	Ile	Cys	Thr	Asp	Asp	Lys	Gly	Val	Phe	Ala	Thr	His	Leu	Ser	Gln
		290				295					300				
Glu	Tyr	Gln	Leu	Ala	Ala	Glu	Thr	Phe	Asn	Leu	Thr	Gln	Ser	Gln	Val
305					310					315					320
Trp	Asp	Leu	Ser	Tyr	Glu	Ser	Ile	Asn	Tyr	Ile	Phe	Ala	Ser	Asp	Ser
				325					330					335	
Thr	Arg	Ser	Glu	Leu	Arg	Lys	Lys	Trp	Asn	His	Leu	Lys	Pro	Arg	Val
			340					345					350		
Leu	His	Ile													
		355													

<210> 47

<211> 1835

<212> DNA

<213> Homosapien

<400> 47

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 gaggaacagg aagaccccaa agactactgc aagggcggct accaccctgt gaagatcggc 240
 gacgtgttca atgggcggta ccacgtggtg cgcaaactgg gctggggcca cttctccacc 300
 gtctggctct gctgggacat ccagcgcaag cgctttgtgg ccctcaaagt ggtgaagagt 360
 gcggggcatt acacggagac agctgtggat gagatcaagc tcctgaaatg tgtccgggac 420

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aggcagggtgc tgcacggcct ggactacctc cacaccaagt gcaagatcat ccacacggac 660
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cggcagtacc gggccgtcga ggtgctgac ggcgcgcaat acggcccccc ggcagacatc 1260
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gacatcccc cagccttcgc cctctcaggc cgctattccc gggagtctt caaccggaga 1440
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ccctaggccc ggctgtggct ccacctccag ctctccgtgc cttagggaa aagcgggaca 1680
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<210> 48

<211> 533

<212> PRT

<213> Homosapien

<400> 48

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Met Ser Ala Ser Thr Gly Gly Gly Gly Asp Ser Gly Gly Ser Gly Gly
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Ser Ser Ser Ser Ser Gln Ala Ser Cys Gly Pro Glu Ser Ser Gly Ser
 20          25          30
Glu Leu Ala Leu Ala Thr Pro Val Pro Gln Met Leu Gln Gly Leu Leu
 35          40          45
Gly Ser Asp Asp Glu Glu Gln Glu Asp Pro Lys Asp Tyr Cys Lys Gly
 50          55          60
Gly Tyr His Pro Val Lys Ile Gly Asp Val Phe Asn Gly Arg Tyr His
 65          70          75          80
Val Val Arg Lys Leu Gly Trp Gly His Phe Ser Thr Val Trp Leu Cys
 85          90          95
Trp Asp Ile Gln Arg Lys Arg Phe Val Ala Leu Lys Val Val Lys Ser
 100          105          110
Ala Gly His Tyr Thr Glu Thr Ala Val Asp Glu Ile Lys Leu Leu Lys
 115          120          125
Cys Val Arg Asp Ser Asp Pro Ser Asp Pro Lys Arg Glu Thr Ile Val
 130          135          140
Gln Leu Ile Asp Asp Phe Arg Ile Ser Gly Val Asn Gly Val His Val
 145          150          155          160
Cys Met Val Leu Glu Val Leu Gly His Gln Leu Leu Lys Trp Ile Ile
 165          170          175
Lys Ser Asn Tyr Gln Gly Leu Pro Val Pro Cys Val Lys Ser Ile Val
 180          185          190
Arg Gln Val Leu His Gly Leu Asp Tyr Leu His Thr Lys Cys Lys Ile
 195          200          205
Ile His Thr Asp Ile Lys Pro Glu Asn Ile Leu Leu Cys Val Gly Asp
 210          215          220
Ala Tyr Ile Arg Arg Leu Ala Ala Glu Ala Thr Glu Trp Gln Gln Ala
 225          230          235          240

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Gly Ala Pro Pro Pro Ser Arg Ser Ile Val Ser Thr Ala Pro Gln Glu
 245 250 255
 Val Leu Thr Gly Lys Leu Ser Lys Asn Lys Arg Lys Lys Met Arg Arg
 260 265 270
 Lys Arg Lys Gln Gln Lys Arg Leu Leu Glu Glu Arg Leu Arg Asp Leu
 275 280 285
 Gln Arg Leu Glu Ala Met Glu Ala Ala Thr Gln Ala Glu Asp Ser Gly
 290 295 300
 Leu Arg Leu Asp Gly Gly Ser Gly Ser Thr Ser Ser Ser Gly Phe Ser
 305 310 315 320
 Gly Ser Leu Phe Ser Pro Ala Ser Cys Ser Ile Leu Ser Gly Ser Ser
 325 330 335
 Asn Gln Arg Glu Thr Gly Gly Leu Leu Ser Pro Ser Thr Pro Phe Gly
 340 345 350
 Ala Ser Asn Leu Leu Val Asn Pro Leu Glu Pro Gln Asn Ala Asp Lys
 355 360 365
 Ile Lys Ile Lys Ile Ala Asp Leu Gly Asn Ala Cys Trp Val His Lys
 370 375 380
 His Phe Thr Glu Asp Ile Gln Thr Arg Gln Tyr Arg Ala Val Glu Val
 385 390 395 400
 Leu Ile Gly Ala Glu Tyr Gly Pro Pro Ala Asp Ile Trp Ser Thr Ala
 405 410 415
 Cys Met Ala Phe Glu Leu Ala Thr Gly Asp Tyr Leu Phe Glu Pro His
 420 425 430
 Ser Gly Glu Asp Tyr Ser Arg Asp Glu Asp His Ile Ala His Ile Val
 435 440 445
 Glu Leu Leu Gly Asp Ile Pro Pro Ala Phe Ala Leu Ser Gly Arg Tyr
 450 455 460
 Ser Arg Glu Phe Phe Asn Arg Arg Gly Glu Leu Arg His Ile His Asn
 465 470 475 480
 Leu Lys His Trp Gly Leu Tyr Glu Val Leu Met Glu Lys Tyr Glu Trp
 485 490 495
 Pro Leu Glu Gln Ala Thr Gln Phe Ser Ala Phe Leu Leu Pro Met Met
 500 505 510
 Glu Tyr Ile Pro Glu Lys Arg Ala Ser Ala Ala Asp Cys Leu Gln His
 515 520 525
 Pro Trp Leu Asn Pro
 530

<210> 49
 <211> 1247
 <212> DNA
 <213> Homosapien

<400> 49
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 cctgacatta gaggagctcc agcagggcca ggaggctgcc cgcgcgctgg aggacatgat 180
 gacgctgagt gctcagaccc tgggtccgagc cgagggtggac gagctctacg aggaagtgcg 240
 tcccctgggc cagggtcgct atggccgcgt ccttctggtc acccatcgct agaaaggcac 300
 acccctggca ctgaagcagc tcccgaaacc ccgcacgtcc ctccgtggct tcctgtacga 360
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 catcgagtgc gcacactcct acagcttccct gacggagccc gtcctgcacg gggacctcat 480
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 ggagaacgct ctggtgtgag acccggcctg ccggcgcttc aagctgaccg acttcggcca 660
 caccaggcct cgcgggacgc tgctgcgcct ggccggggccg cccatccctt acacggcccc 720
 cgagctctgc gcgccccgc cgctccccga gggcctgccc attcagcccg ccctggacgc 780
 ctgggcgctg ggcgtcctgc tcttctgcct cctcacgggc tacttccctt gggaccggcc 840
 cctggccgag gccgaccctt tctacagga cttctcatc tggcaggcgt cgggcccaggc 900

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gctgctggac cctcaccccc gaaggaggag cgctgtgatc gccatcaggg agcacctggg 1020
gcgcccctgg aggcagcggg agggcgaggc ggaggcagtg ggagcgggtg aagaggaggc 1080
tgggcagtgga ggaggccccg ggggatgcag aaagggaagc cgccccaccc gagggcccca 1140
agttcaacgg cttttggtgt ctctcgggtg tgttttcac ccatggggctt gggattcccc 1200
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<210> 50

<211> 348

<212> PRT

<213> Homosapien

<400> 50

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Met Pro Gly Lys Gln Ser Glu Glu Gly Pro Ala Glu Ala Gly Ala Ser
1          5          10          15
Glu Asp Ser Glu Glu Gly Leu Gly Leu Thr Leu Glu Leu
20          25          30
Gln Gln Gly Gln Glu Ala Ala Arg Ala Leu Glu Asp Met Met Thr Leu
35          40          45
Ser Ala Gln Thr Leu Val Arg Ala Glu Val Asp Glu Leu Tyr Glu Glu
50          55          60
Val Arg Pro Leu Gly Gln Gly Arg Tyr Gly Arg Val Leu Leu Val Thr
65          70          75          80
His Arg Gln Lys Gly Thr Pro Leu Ala Leu Lys Gln Leu Pro Lys Pro
85          90          95
Arg Thr Ser Leu Arg Gly Phe Leu Tyr Glu Phe Cys Val Gly Leu Ser
100          105          110
Leu Gly Ala His Ser Ala Ile Val Thr Ala Tyr Gly Ile Gly Ile Glu
115          120          125
Ser Ala His Ser Tyr Ser Phe Leu Thr Glu Pro Val Leu His Gly Asp
130          135          140
Leu Met Ala Phe Ile Gln Pro Lys Val Gly Leu Pro Gln Pro Ala Val
145          150          155          160
His Arg Cys Ala Ala Gln Leu Ala Ser Ala Leu Glu Tyr Ile His Ala
165          170          175
Arg Gly Leu Val Tyr Arg Asp Leu Lys Pro Glu Asn Val Leu Val Cys
180          185          190
Asp Pro Ala Cys Arg Arg Phe Lys Leu Thr Asp Phe Gly His Thr Arg
195          200          205
Pro Arg Gly Thr Leu Leu Arg Leu Ala Gly Pro Pro Ile Pro Tyr Thr
210          215          220
Ala Pro Glu Leu Cys Ala Pro Pro Pro Leu Pro Glu Gly Leu Pro Ile
225          230          235          240
Gln Pro Ala Leu Asp Ala Trp Ala Leu Gly Val Leu Leu Phe Cys Leu
245          250          255
Leu Thr Gly Tyr Phe Pro Trp Asp Arg Pro Leu Ala Glu Ala Asp Pro
260          265          270
Phe Tyr Glu Asp Phe Leu Ile Trp Gln Ala Ser Gly Gln Pro Arg Asp
275          280          285
Arg Pro Gln Pro Trp Phe Gly Leu Ala Pro Ala Ala Asp Ala Leu Leu
290          295          300
Arg Gly Leu Leu Asp Pro His Pro Arg Arg Arg Ser Ala Val Ile Ala
305          310          315          320
Ile Arg Glu His Leu Gly Arg Pro Trp Arg Gln Arg Glu Gly Glu Ala
325          330          335
Glu Ala Val Gly Ala Val Glu Glu Glu Ala Gly Gln
340          345

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<210> 51

<211> 1881

<212> DNA

<213> Homosapien

<400> 51

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aattgaaaga tttttttttc ttacaaagaa cacgttatac gtcattttaa ttgccaaata 180
tcaaatagtt tattctatct cactttctag ggaaaaaac caactgctcc aaaagaatgt 240
gtttttctcc cattctggaa atcaacatgc agtctgaatc taacattaca gtgcgagatg 300
acattgatga catcaacacc aatatgtacc aaccactatc atatccgtta agctttcaag 360
tgtctctcac cggattttct atgttagaaa ttgtgttggg acttggcagc aacctcactg 420
tattggtact ttactgcatg aaatccaact taatcaactc tgtcagtaac attattacaa 480
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tcctttctgt ttactggag agtaacactg ctctcatttg ctgtttccat gaggcttgtg 600
tatcttttgc aagtgtctca acagcaatca acgtttttgc tatcactttg gacagatatg 660
acatctctgt aaaacctgca aaccgaattc tgacaatggg cagagctgta atgttaatga 720
tatccatttg gattttttct tttttctctt tcttgattcc ttttattgag gtaaattttt 780
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aatactacac tgaactggga atgtattatc acctgttagt acagatccca atattctttt 900
tcactgttgt agtaatgtta atcacatata ccaaaatact tcaggctctt aatattcgaa 960
taggcacaag attttcaaca gggcagaaga agaaagcaag aaagaaaaag acaattttct 1020
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gtgaacgacg agaaagacaa aagagagtct tcaggatgtc tttattgatt atttctacat 1200
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<210> 52

<211> 433

<212> PRT

<213> Homosapien

<400> 52

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 20           25           30
Pro Leu Ser Tyr Pro Leu Ser Phe Gln Val Ser Leu Thr Gly Phe Leu
 35           40           45
Met Leu Glu Ile Val Leu Gly Leu Gly Ser Asn Leu Thr Val Leu Val
 50           55           60
Leu Tyr Cys Met Lys Ser Asn Leu Ile Asn Ser Val Ser Asn Ile Ile
 65           70           75           80
Thr Met Asn Leu His Val Leu Asp Val Ile Ile Cys Val Gly Cys Ile
 85           90           95
Pro Leu Thr Ile Val Ile Leu Leu Leu Ser Leu Glu Ser Asn Thr Ala
100           105           110
Leu Ile Cys Cys Phe His Glu Ala Cys Val Ser Phe Ala Ser Val Ser
115           120           125
Thr Ala Ile Asn Val Phe Ala Ile Thr Leu Asp Arg Tyr Asp Ile Ser
130           135           140

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Val Lys Pro Ala Asn Arg Ile Leu Thr Met Gly Arg Ala Val Met Leu
 145 150 155 160
 Met Ile Ser Ile Trp Ile Phe Ser Phe Phe Ser Phe Leu Ile Pro Phe
 165 170 175
 Ile Glu Val Asn Phe Phe Ser Leu Gln Ser Gly Asn Thr Trp Glu Asn
 180 185 190
 Lys Thr Leu Leu Cys Val Ser Thr Asn Glu Tyr Tyr Thr Glu Leu Gly
 195 200 205
 Met Tyr Tyr His Leu Leu Val Gln Ile Pro Ile Phe Phe Phe Thr Val
 210 215 220
 Val Val Met Leu Ile Thr Tyr Thr Lys Ile Leu Gln Ala Leu Asn Ile
 225 230 235 240
 Arg Ile Gly Thr Arg Phe Ser Thr Gly Gln Lys Lys Lys Ala Arg Lys
 245 250 255
 Lys Lys Thr Ile Ser Leu Thr Thr Gln His Glu Ala Thr Asp Met Ser
 260 265 270
 Gln Ser Ser Gly Gly Arg Asn Val Phe Gly Val Arg Thr Ser Val
 275 280 285
 Ser Val Ile Ile Ala Leu Arg Arg Ala Val Lys Arg His Arg Glu Arg
 290 295 300
 Arg Glu Arg Gln Lys Arg Val Phe Arg Met Ser Leu Leu Ile Ile Ser
 305 310 315 320
 Thr Phe Leu Leu Cys Trp Thr Pro Ile Ser Val Leu Asn Thr Thr Ile
 325 330 335
 Leu Cys Leu Gly Pro Ser Asp Leu Leu Val Lys Leu Arg Leu Cys Phe
 340 345 350
 Leu Val Met Ala Tyr Gly Thr Thr Ile Phe His Pro Leu Leu Tyr Ala
 355 360 365
 Phe Thr Arg Gln Lys Phe Gln Lys Val Leu Lys Ser Lys Met Lys Lys
 370 375 380
 Arg Val Val Ser Ile Val Glu Ala Asp Pro Leu Pro Asn Asn Ala Val
 385 390 395 400
 Ile His Asn Ser Trp Ile Asp Pro Lys Arg Asn Lys Lys Ile Thr Phe
 405 410 415
 Glu Asp Ser Glu Ile Arg Glu Lys Arg Leu Val Pro Gln Val Val Thr
 420 425 430
 Asp

<210> 53
 <211> 1626
 <212> DNA
 <213> Homosapien

<220>
 <221> misc_feature
 <222> (1)...(1626)
 <223> n = A,T,C or G

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 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ggcgtccgccg gccgctgggc cgctgcctga 180
 gccaggaggg cgcagcgcga gtcgccactt cgtcttcacg gattcccagc ccagctgcgt 240
 ggtgggtgact ggttttgggc ccttccggca gcacttgggt aattccagct gggaagcagt 300
 gaaggagctc tccaagctgg gcctggggaa tgaaacagtg gtgcagctgc ggactctgga 360
 gctgcctgta gattacaggg aggctaagcg gagggtcacc ggaatctggg aagatcatca 420
 gccgcaactc gtcgtgcatg tgggcatgga caccgccgcc aaggcgatca ttctggaaca 480
 gtctggcaag aaccaaggct accgggacgc cgacatccgc agcttctggc ccgagggcgg 540
 cgtgtgccta cctggcagcc cagacgtgct ggagtcaggg gtctgcatga aggcagctctg 600

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caagcgcgta gctgtggagg gtgtcgacgt gatcttttcc cgagatgcag gcagatacgt 660
ctgtgattat acctattacc tgtctctgca tcatggaaaag ggctgcgcgg cactcatcca 720
tgtccctcca ctatcgcgcg ggctcccgcc cagcctgctg ggaagagcct tgagaggtca 780
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<210> 54

<211> 196

<212> PRT

<213> Homosapien

<400> 54

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  1          5          10          15
Arg Gln His Leu Val Asn Ser Ser Trp Glu Ala Val Lys Glu Leu Ser
      20          25          30
Lys Leu Gly Leu Gly Asn Glu Thr Val Val Gln Leu Arg Thr Leu Glu
      35          40          45
Leu Pro Val Asp Tyr Arg Glu Ala Lys Arg Arg Val Thr Gly Ile Trp
      50          55          60
Glu Asp His Gln Pro Gln Leu Val Val His Val Gly Met Asp Thr Ala
      65          70          75          80
Ala Lys Ala Ile Ile Leu Glu Gln Ser Gly Lys Asn Gln Gly Tyr Arg
      85          90          95
Asp Ala Asp Ile Arg Ser Phe Trp Pro Glu Gly Gly Val Cys Leu Pro
      100          105          110
Gly Ser Pro Asp Val Leu Glu Ser Gly Val Cys Met Lys Ala Val Cys
      115          120          125
Lys Arg Val Ala Val Glu Gly Val Asp Val Ile Phe Ser Arg Asp Ala
      130          135          140
Gly Arg Tyr Val Cys Asp Tyr Thr Tyr Tyr Leu Ser Leu His His Gly
      145          150          155          160
Lys Gly Cys Ala Ala Leu Ile His Val Pro Pro Leu Ser Arg Gly Leu
      165          170          175
Pro Ala Ser Leu Leu Gly Arg Ala Leu Arg Gly His His Pro Ala Asn
      180          185          190
Ala Gly Arg Gly
      195

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<210> 55

<211> 2335

<212> DNA

<213> Homosapien

<400> 55

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<210> 56

<211> 695

<212> PRT

<213> Homosapien

<400> 56

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Met Ala Glu Ala Pro Pro Arg Arg Leu Gly Leu Gly Pro Pro Pro Gly
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Asp Ala Pro Arg Ala Glu Leu Val Ala Leu Thr Ala Val Gln Ser Glu
20           25           30
Gln Gly Glu Ala Gly Gly Gly Gly Ser Pro Arg Arg Leu Gly Leu Leu
35           40           45
Gly Ser Pro Leu Pro Pro Gly Ala Pro Leu Pro Gly Pro Gly Ser Gly
50           55           60
Ser Gly Ser Ala Cys Gly Gln Arg Ser Ser Ala Ala His Lys Arg Tyr
65           70           75           80
Arg Arg Leu Gln Asn Trp Val Tyr Asn Val Leu Glu Arg Pro Arg Gly
85           90           95
Trp Ala Phe Val Tyr His Val Phe Ile Phe Leu Leu Val Phe Ser Cys
100          105          110
Leu Val Leu Ser Val Leu Ser Thr Ile Gln Glu His Gln Glu Leu Ala
115          120          125

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Asn Glu Cys Leu Leu Ile Leu Glu Phe Val Met Ile Val Val Phe Gly
 130 135 140
 Leu Glu Tyr Ile Val Arg Val Trp Ser Ala Gly Cys Cys Cys Arg Tyr
 145 150 155 160
 Arg Gly Trp Gln Gly Arg Phe Arg Phe Ala Arg Lys Pro Phe Cys Val
 165 170 175
 Ile Asp Phe Ile Val Phe Val Ala Ser Val Ala Val Ile Ala Ala Gly
 180 185 190
 Thr Gln Gly Asn Ile Phe Ala Thr Ser Ala Leu Arg Ser Met Arg Phe
 195 200 205
 Leu Gln Ile Leu Arg Met Val Arg Met Asp Arg Arg Gly Gly Thr Trp
 210 215 220
 Lys Leu Leu Gly Ser Val Val Tyr Ala His Ser Lys Glu Leu Ile Thr
 225 230 235 240
 Ala Trp Tyr Ile Gly Phe Leu Val Leu Ile Phe Ala Ser Phe Leu Val
 245 250 255
 Tyr Leu Ala Glu Lys Asp Ala Asn Ser Asp Phe Ser Ser Tyr Ala Asp
 260 265 270
 Ser Leu Trp Trp Gly Thr Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp
 275 280 285
 Lys Thr Pro His Thr Trp Leu Gly Arg Val Leu Ala Ala Gly Phe Ala
 290 295 300
 Leu Leu Gly Ile Ser Phe Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser
 305 310 315 320
 Gly Phe Ala Leu Lys Val Gln Glu Gln His Arg Gln Lys His Phe Glu
 325 330 335
 Lys Arg Arg Met Pro Ala Ala Asn Leu Ile Gln Ala Ala Trp Arg Leu
 340 345 350
 Tyr Ser Thr Asp Met Ser Arg Ala Tyr Leu Thr Ala Thr Trp Tyr Tyr
 355 360 365
 Tyr Asp Ser Ile Leu Pro Ser Phe Arg Glu Leu Ala Leu Leu Phe Glu
 370 375 380
 His Val Gln Arg Ala Arg Asn Gly Gly Leu Arg Pro Leu Glu Val Arg
 385 390 395 400
 Arg Ala Pro Val Pro Asp Gly Ala Pro Ser Arg Tyr Pro Pro Val Ala
 405 410 415
 Thr Cys His Arg Pro Gly Ser Thr Ser Phe Cys Pro Gly Glu Ser Ser
 420 425 430
 Arg Met Gly Ile Lys Asp Arg Ile Arg Met Gly Ser Ser Gln Arg Arg
 435 440 445
 Thr Gly Pro Ser Lys Gln Gln Leu Ala Pro Pro Thr Met Pro Thr Ser
 450 455 460
 Pro Ser Ser Glu Gln Val Gly Glu Ala Thr Ser Pro Thr Lys Val Gln
 465 470 475 480
 Lys Ser Trp Ser Phe Asn Asp Arg Thr Arg Phe Arg Ala Ser Leu Arg
 485 490 495
 Leu Lys Pro Arg Thr Ser Ala Glu Asp Ala Pro Ser Glu Glu Val Ala
 500 505 510
 Glu Glu Lys Ser Tyr Gln Cys Glu Leu Thr Val Asp Asp Ile Met Pro
 515 520 525
 Ala Val Lys Thr Val Ile Arg Ser Ile Arg Ile Leu Lys Phe Leu Val
 530 535 540
 Ala Lys Arg Lys Phe Lys Glu Thr Leu Arg Pro Tyr Asp Val Lys Asp
 545 550 555 560
 Val Ile Glu Gln Tyr Ser Ala Gly His Leu Asp Met Leu Gly Arg Ile
 565 570 575
 Lys Ser Leu Gln Thr Arg Val Asp Gln Ile Val Gly Arg Gly Pro Gly
 580 585 590
 Asp Arg Lys Ala Arg Glu Lys Gly Asp Lys Gly Pro Ser Asp Ala Glu
 595 600 605
 Val Val Asp Glu Ile Ser Met Met Gly Arg Val Val Lys Val Glu Lys

610		615		620	
Gln Val Gln Ser Ile	Glu His Lys Leu Asp	Leu Leu Leu Gly Phe Tyr			
625	630	635	640		
Ser Arg Cys Leu Arg	Ser Gly Thr Ser Ala Ser	Leu Gly Ala Val Gln			
645	650	655			
Val Pro Leu Phe Asp	Pro Asp Ile Thr Ser Asp	Tyr His Ser Pro Val			
660	665	670			
Asp His Glu Asp Ile	Ser Val Ser Ala Gln	Thr Leu Ser Ile Ser Arg			
675	680	685			
Ser Val Ser Thr Asn	Met Asp				
690	695				

<210> 57

<211> 3758

<212> DNA

<213> Homosapien

<400> 57

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cccagagagg ctgctgcaggc gggaagacgc cagaggccag cttcgggtccc ccttctgtct 180
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ctcactccag aagaatttga ccaactccag aatatctcag aatatctctc caagaagata 600
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ccgattagct atgatgtctt caagctgttc atgagggcgt acctggagggt ggaccttccc 720
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<210> 58

<211> 791

<212> PRT

<213> Homosapien

<400> 58

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20          25          30
Thr Glu Phe Asn Glu Gly Gly Ser Leu Lys Gln Tyr Asp Pro His Glu
35          40          45
Pro Ile Ser Tyr Asp Val Phe Lys Leu Phe Met Arg Ala Tyr Leu Glu
50          55          60
Val Asp Leu Pro Gln Pro Leu Ser Thr His Leu Phe Leu Ala Phe Ser
65          70          75          80
Gln Lys Pro Arg His Glu Thr Ser Asp His Pro Thr Glu Gly Ala Ser
85          90          95
Asn Ser Glu Ala Asn Ser Ala Asp Thr Asn Ile Gln Asn Ala Asp Asn
100         105         110
Ala Thr Lys Ala Asp Glu Ala Cys Ala Pro Asp Thr Glu Ser Asn Met
115         120         125
Ala Glu Lys Gln Ala Pro Ala Glu Asp Gln Val Ala Ala Thr Pro Leu
130         135         140
Glu Pro Pro Val Pro Arg Ser Ser Ser Ser Glu Ser Pro Val Val Tyr
145         150         155         160
Leu Lys Asp Val Val Cys Tyr Leu Ser Leu Leu Glu Thr Gly Arg Pro
165         170         175
Gln Asp Lys Leu Glu Phe Met Phe Arg Leu Tyr Asp Ser Asp Glu Asn
180         185         190
Gly Leu Leu Asp Gln Ala Glu Met Asp Cys Ile Val Asn Gln Met Leu
195         200         205
His Ile Ala Gln Tyr Leu Glu Trp Asp Pro Thr Glu Leu Arg Pro Ile
210         215         220
Leu Lys Glu Met Leu Gln Gly Met Asp Tyr Asp Arg Asp Gly Phe Val
225         230         235         240
Ser Leu Gln Glu Trp Val His Gly Gly Met Thr Thr Ile Pro Leu Leu
245         250         255
Val Leu Leu Gly Met Asp Asp Ser Gly Ser Lys Gly Asp Gly Gly His

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Trp Met Gln Pro Cys Cys Thr Ile Lys Ile Thr His Lys Asn Gln Ala
 755 760 765
 Pro Met Met Met Gly Pro Pro Gln Lys Ser Ser Phe Phe Ser Leu Arg
 770 775 780
 Arg Lys Ser Arg Ser Lys Asp
 785 790

<210> 59
 <211> 1270
 <212> DNA
 <213> Homosapien

<400> 59
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 gggacctgga ggcctccaac gactccttcc tgcttcctgg acaggactat ggctgtgcag 180
 ggatcccaga gaagacttct gggctccctc aactccaccc ccacagccat cccccagctg 240
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 aagaaccgga acctgcactc acccatgtac tgcttcatct gctgcctggc cttgtcggac 420
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<210> 60
 <211> 317
 <212> PRT
 <213> Homosapien

<400> 60
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 Thr Pro Thr Ala Ile Pro Gln Leu Gly Leu Ala Ala Asn Gln Thr Gly
 20 25 30
 Ala Arg Cys Leu Glu Val Ser Ile Ser Asp Gly Leu Phe Leu Ser Leu
 35 40 45
 Gly Leu Val Ser Leu Val Glu Asn Ala Leu Val Val Ala Thr Ile Ala
 50 55 60
 Lys Asn Arg Asn Leu His Ser Pro Met Tyr Cys Phe Ile Cys Cys Leu
 65 70 75 80
 Ala Leu Ser Asp Leu Leu Val Ser Gly Ser Asn Val Leu Glu Thr Ala
 85 90 95
 Val Ile Leu Leu Leu Glu Ala Gly Ala Leu Val Ala Arg Ala Ala Val
 100 105 110
 Leu Gln Gln Leu Asp Asn Val Ile Asp Val Ile Thr Cys Ser Ser Met
 115 120 125
 Leu Ser Ser Leu Cys Phe Leu Gly Ala Ile Ala Val Asp Arg Tyr Ile
 130 135 140

Ser Ile Phe Tyr Ala Leu Arg Tyr His Ser Ile Val Thr Leu Pro Arg
 145 150 155 160
 Ala Arg Gln Ala Val Ala Ala Ile Trp Val Ala Ser Val Val Phe Ser
 165 170 175
 Thr Leu Phe Ile Ala Tyr Tyr Asp His Val Ala Val Leu Leu Cys Leu
 180 185 190
 Val Val Phe Phe Leu Ala Met Leu Val Leu Met Ala Val Leu Tyr Val
 195 200 205
 His Met Leu Ala Arg Ala Cys Gln His Ala Gln Gly Ile Ala Arg Leu
 210 215 220

His Lys Arg Gln Arg Pro Val His Gln Gly Phe Gly Leu Lys Gly Ala
 225 230 235 240
 Val Thr Leu Thr Ile Leu Leu Gly Ile Phe Phe Leu Cys Trp Gly Pro
 245 250 255
 Phe Phe Leu His Leu Thr Leu Ile Val Leu Cys Pro Glu His Pro Thr
 260 265 270
 Cys Gly Cys Ile Phe Lys Asn Phe Asn Leu Phe Leu Ala Leu Ile Ile
 275 280 285
 Cys Asn Ala Ile Ile Asp Pro Leu Ile Tyr Ala Phe His Ser Gln Glu
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 Leu Arg Arg Thr Leu Lys Glu Val Leu Thr Cys Ser Trp
 305 310 315

<210> 61
 <211> 1599
 <212> DNA
 <213> Homosapien

<400> 61
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 attaagaagg agagtaaccg gcagagggtt ggattggagc tgattgcctc ggagaatttc 180
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<210> 62
 <211> 483

<212> PRT

<213> Homosapien

<400> 62

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Glu Leu Ile Ala Ser Glu Asn Phe Ala Ser Arg Ala Val Leu Glu Ala
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Leu Gly Ser Cys Leu Asn Asn Lys Tyr Ser Glu Gly Tyr Pro Gly Gln
65          70          75          80
Arg Tyr Tyr Gly Gly Thr Glu Phe Ile Asp Glu Leu Glu Thr Leu Cys
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Gln Lys Arg Ala Leu Gln Ala Tyr Lys Leu Asp Pro Gln Cys Trp Gly
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Val Asn Val Gln Pro Tyr Ser Gly Ser Pro Ala Asn Phe Ala Val Tyr
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Thr Ala Leu Val Glu Pro His Gly Arg Ile Met Gly Leu Asp Leu Pro
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Asp Gly Gly His Leu Thr His Gly Phe Met Thr Asp Lys Lys Lys Ile
145          150          155          160
Ser Ala Thr Ser Ile Phe Phe Glu Ser Met Pro Tyr Lys Val Asn Pro
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Asp Thr Gly Tyr Ile Asn Tyr Asp Gln Leu Glu Glu Asn Ala Arg Leu
      180          185          190
Phe His Pro Lys Leu Ile Ile Ala Gly Thr Ser Cys Tyr Ser Arg Asn
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Leu Glu Tyr Ala Arg Leu Arg Lys Ile Ala Asp Glu Asn Gly Ala Tyr
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Leu Met Ala Asp Met Ala His Ile Ser Gly Leu Val Ala Ala Gly Val
225          230          235          240
Val Pro Ser Pro Phe Glu His Cys His Val Val Thr Thr Thr Thr His
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Lys Thr Leu Arg Gly Cys Arg Ala Gly Met Ile Phe Tyr Arg Lys Gly
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Val Lys Ser Val Asp Pro Lys Thr Gly Lys Glu Ile Leu Tyr Asn Leu
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Glu Ser Leu Ile Asn Ser Ala Val Phe Pro Gly Leu Gln Gly Gly Pro
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His Asn His Ala Ile Ala Gly Val Ala Val Ala Leu Lys Gln Ala Met
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Thr Leu Glu Phe Lys Val Tyr Gln His Gln Val Val Ala Asn Cys Arg
      325          330          335
Ala Leu Ser Glu Ala Leu Thr Glu Leu Gly Tyr Lys Ile Val Thr Gly
      340          345          350
Gly Ser Asp Asn His Leu Ile Leu Val Asp Leu Arg Ser Lys Gly Thr
      355          360          365
Asp Gly Gly Arg Ala Glu Lys Val Leu Glu Ala Cys Ser Ile Ala Cys
370          375          380
Asn Lys Asn Thr Cys Pro Gly Asp Arg Ser Ala Leu Arg Pro Ser Gly
385          390          395          400
Leu Arg Leu Gly Thr Pro Ala Leu Thr Ser Arg Gly Leu Leu Glu Lys
      405          410          415
Asp Phe Gln Lys Val Ala His Phe Ile His Arg Gly Ile Glu Leu Thr
      420          425          430
Leu Gln Ile Gln Ser Asp Thr Gly Val Arg Ala Thr Leu Lys Glu Phe
      435          440          445
Lys Glu Arg Leu Ala Gly Asp Lys Tyr Gln Ala Ala Val Gln Ala Leu

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 <212> DNA
 <213> Homosapien

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<210> 64
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 <212> PRT
 <213> Homosapien

<400> 64
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 Met Val Gln Glu Arg Glu Lys Asp Ile Leu Thr Ala Ile Ala Ala Asp
 35 40 45
 Leu Cys Lys Ser Glu Phe Asn Val Tyr Ser Gln Glu Val Ile Thr Val
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<210> 65
<211> 1487
<212> DNA
<213> Homosapien
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66/136

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<210> 66

<211> 392

<212> PRT

<213> Homosapien

<400> 66

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Leu Pro Pro Arg Ile Met Ala Ala Gly Gly Leu Gln Met Ile Gly Ser
35     40     45
Met Ser Lys Asp Met Tyr Gln Ile Met Asp Glu Ile Lys Glu Gly Ile
50     55     60
Gln Tyr Val Phe Gln Thr Arg Asn Pro Leu Thr Leu Val Ile Ser Gly
65     70     75     80
Ser Gly His Cys Ala Leu Glu Ala Ala Leu Val Asn Val Leu Glu Pro
85     90     95
Gly Asp Ser Phe Leu Val Gly Ala Asn Gly Ile Trp Gly Gln Arg Ala
100    105    110
Val Asp Ile Gly Glu Arg Ile Gly Ala Arg Val His Pro Met Thr Lys
115    120    125
Asp Pro Gly Gly His Tyr Thr Leu Gln Glu Val Glu Glu Gly Leu Ala
130    135    140
Gln His Lys Pro Val Leu Leu Phe Leu Thr His Gly Glu Ser Ser Thr
145    150    155    160
Gly Val Leu Gln Pro Leu Asp Gly Phe Gly Glu Leu Cys His Arg Tyr
165    170    175
Lys Cys Leu Leu Val Asp Ser Val Ala Ser Leu Gly Gly Thr Pro
180    185    190
Leu Tyr Met Asp Arg Gln Gly Ile Asp Ile Leu Tyr Ser Gly Ser Gln
195    200    205
Lys Ala Leu Asn Ala Pro Pro Gly Thr Ser Leu Ile Ser Phe Ser Asp
210    215    220
Lys Ala Lys Lys Lys Met Tyr Ser Arg Lys Thr Lys Pro Phe Ser Phe
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Tyr Leu Asp Ile Lys Trp Leu Ala Asn Phe Trp Gly Cys Asp Asp Gln

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68/136

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<210> 68

<211> 1885

<212> PRT

<213> Homosapien

<400> 68

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65          70          75          80
Glu Lys His Thr Glu Gln Ser Pro Thr Asp Ala Tyr Gly Val Ile Asn
85          90          95
Phe Gln Gly Gly Ser His Ser Tyr Arg Ala Lys Tyr Val Arg Leu Ser
100          105          110
Tyr Asp Thr Lys Pro Glu Val Ile Leu Gln Leu Leu Leu Lys Glu Trp
115          120          125
Gln Met Glu Leu Pro Lys Leu Val Ile Ser Val His Gly Gly Met Gln
130          135          140
Lys Phe Glu Leu His Pro Arg Ile Lys Gln Leu Leu Gly Lys Gly Leu
145          150          155          160
Ile Lys Ala Ala Val Thr Thr Gly Ala Trp Ile Leu Thr Gly Gly Val
165          170          175
Asn Thr Gly Val Ala Lys His Val Gly Asp Ala Leu Lys Glu His Ala
180          185          190
Ser Arg Ser Ser Arg Lys Ile Cys Thr Ile Gly Ile Ala Pro Trp Gly

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195	200	205
Val Ile Glu Asn Arg Asn Asp	Leu Val Gly Arg Asp	Val Val Ala Pro
210	215	220
Tyr Gln Thr Leu Leu Asn Pro	Leu Ser Lys Leu Asn Val	Leu Asn Asn
225	230	235
Leu His Ser His Phe Ile Leu	Val Asp Asp Gly Thr Val	Gly Lys Tyr
245	250	255
Gly Ala Glu Val Arg Leu Arg	Arg Glu Leu Glu Lys Thr	Ile Asn Gln
260	265	270
Gln Arg Ile His Ala Arg Ile	Gly Gln Gly Val Pro Val	Val Val Ala Leu
275	280	285
Ile Phe Glu Gly Gly Pro Asn	Val Ile Leu Thr Val Leu	Glu Tyr Leu
290	295	300
Gln Glu Ser Pro Pro Val Pro	Val Val Val Cys Glu Gly	Thr Gly Arg
305	310	315
Ala Ala Asp Leu Leu Ala Tyr	Ile His Lys Gln Thr Glu	Glu Gly Gly
325	330	335
Asn Leu Pro Asp Ala Ala Gly	His Asp Ile Ile Ser Thr	Ile Lys Lys
340	345	350
Thr Phe Asn Phe Gly Gln Asn	Glu Ala Leu His Leu Phe	Gln Thr Leu
355	360	365
Met Glu Cys Met Lys Arg Lys	Glu Leu Ile Thr Val Phe	His Ile Gly
370	375	380
Ser Asp Glu His Gln Asp Ile	Asp Val Ala Ile Leu Thr	Ala Leu Leu
385	390	395
Lys Gly Thr Asn Ala Ser Ala	Phe Asp Gln Leu Ile Leu	Thr Leu Ala
405	410	415
Trp Gly Arg Val Asp Ile Ala	Lys Asn His Val Phe Val	Tyr Gly Gln
420	425	430
Gln Trp Leu Val Gly Ser Leu	Glu Gln Ala Met Leu Asp	Ala Leu Val
435	440	445
Met Asp Arg Val Ala Phe Val	Lys Leu Leu Ile Glu Asn	Gly Val Ser
450	455	460
Met His Lys Phe Leu Thr Ile	Pro Arg Leu Glu Leu Tyr	Asn Thr
465	470	475
Lys Gln Gly Pro Thr Asn Pro	Met Leu Phe His Leu Val	Arg Asp Val
485	490	495
Lys Gln Gly Asn Leu Pro Pro	Gly Tyr Lys Ile Thr Leu	Ile Asp Ile
500	505	510
Gly Leu Val Ile Glu Tyr Leu	Met Gly Gly Thr Tyr Arg	Cys Thr Tyr
515	520	525
Thr Arg Lys Arg Phe Arg Leu	Ile Tyr Asn Ser Leu Gly	Gly Asn Asn
530	535	540
Arg Arg Ser Gly Arg Asn Thr	Ser Ser Ser Thr Pro Gln	Leu Arg Lys
545	550	555
Ser His Glu Ser Phe Gly Asn	Arg Ala Asp Lys Lys Glu	Lys Met Arg
565	570	575
His Asn His Phe Ile Lys Thr	Ala Gln Pro Tyr Arg Pro	Lys Ile Asp
580	585	590
Thr Val Met Glu Glu Gly Lys	Lys Lys Arg Thr Lys Asp	Glu Ile Val
595	600	605
Asp Ile Asp Asp Pro Glu Thr	Lys Arg Phe Pro Tyr Pro	Leu Asn Glu
610	615	620
Leu Leu Ile Trp Ala Cys Leu	Met Lys Arg Gln Val Met	Ala Arg Phe
625	630	635
Leu Trp Gln His Gly Glu Glu	Ser Met Ala Lys Ala Leu	Val Ala Cys
645	650	655
Lys Ile Tyr Arg Ser Met Ala	Tyr Glu Ala Lys Gln Ser	Asp Leu Val
660	665	670
Asp Asp Thr Ser Glu Glu Leu	Lys Gln Tyr Ser Asn Asp	Phe Gly Gln
675	680	685

Leu Ala Val Glu Leu Leu Glu Gln Ser Phe Arg Gln Asp Glu Thr Met
 690 695 700
 Ala Met Lys Leu Leu Thr Tyr Glu Leu Lys Asn Trp Ser Asn Ser Thr
 705 710 715 720
 Cys Leu Lys Leu Ala Val Ser Ser Arg Leu Arg Pro Phe Val Ala His
 725 730 735
 Thr Cys Thr Gln Met Leu Leu Ser Asp Met Trp Met Gly Arg Leu Asn
 740 745 750
 Met Arg Lys Asn Ser Trp Tyr Lys Val Ile Leu Ser Ile Leu Val Pro
 755 760 765
 Pro Ala Ile Leu Leu Leu Glu Tyr Lys Thr Lys Ala Glu Met Ser His
 770 775 780
 Ile Pro Gln Ser Gln Asp Ala His Gln Met Ser Met Asp Asp Ser Glu
 785 790 795 800
 Asn Asn Phe Gln Asn Ile Thr Glu Glu Ile Pro Met Glu Val Phe Lys
 805 810 815
 Glu Val Arg Ile Leu Asp Ser Asn Glu Gly Lys Asn Glu Met Glu Ile
 820 825 830
 Gln Met Lys Ser Lys Lys Leu Pro Ile Thr Arg Lys Phe Tyr Ala Phe
 835 840 845
 Tyr His Ala Pro Ile Val Lys Phe Trp Phe Asn Thr Leu Ala Tyr Leu
 850 855 860
 Gly Phe Leu Met Leu Tyr Thr Phe Val Val Leu Val Gln Met Glu Gln
 865 870 875 880
 Leu Pro Ser Val Gln Glu Trp Ile Val Ile Ala Tyr Ile Phe Thr Tyr
 885 890 895
 Ala Ile Glu Lys Val Arg Glu Ile Phe Met Ser Glu Ala Gly Lys Val
 900 905 910
 Asn Gln Lys Ile Lys Val Trp Phe Ser Asp Tyr Phe Asn Ile Ser Asp
 915 920 925
 Thr Ile Ala Ile Ile Ser Phe Phe Ile Gly Phe Gly Leu Arg Phe Gly
 930 935 940
 Ala Lys Trp Asn Phe Ala Asn Ala Tyr Asp Asn His Val Phe Val Ala
 945 950 955 960
 Gly Arg Leu Ile Tyr Cys Leu Asn Ile Ile Phe Trp Tyr Val Arg Leu
 965 970 975
 Leu Asp Phe Leu Ala Val Asn Gln Gln Ala Gly Pro Tyr Val Met Met
 980 985 990
 Ile Gly Lys Met Val Ala Asn Met Phe Tyr Ile Val Val Ile Met Ala
 995 1000 1005
 Leu Val Leu Leu Ser Phe Gly Val Pro Arg Lys Ala Ile Leu Tyr Pro
 1010 1015 1020
 His Glu Ala Pro Ser Trp Thr Leu Ala Lys Asp Ile Val Phe His Pro
 1025 1030 1035 1040
 Tyr Trp Met Ile Phe Gly Glu Val Tyr Ala Tyr Glu Ile Asp Val Cys
 1045 1050 1055
 Ala Asn Asp Ser Val Ile Pro Gln Ile Cys Gly Pro Gly Thr Trp Leu
 1060 1065 1070
 Thr Pro Phe Leu Gln Ala Val Tyr Leu Phe Val Gln Tyr Ile Ile Met
 1075 1080 1085
 Val Asn Leu Leu Ile Ala Phe Phe Asn Asn Val Tyr Leu Gln Val Lys
 1090 1095 1100
 Ala Ile Ser Asn Ile Val Trp Lys Tyr Gln Arg Tyr His Phe Ile Met
 1105 1110 1115 1120
 Ala Tyr His Glu Lys Pro Val Leu Pro Pro Leu Ile Ile Leu Ser
 1125 1130 1135
 His Ile Val Ser Leu Phe Cys Cys Ile Cys Lys Arg Arg Lys Lys Asp
 1140 1145 1150
 Lys Thr Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp Gln Lys
 1155 1160 1165
 Lys Leu His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe Asn Glu

1170	1175	1180
Lys Asp Asp Lys Phe His Ser Gly Ser Glu Glu Arg Ile Arg Val Thr		
1185	1190	1195
Phe Glu Arg Val Glu Gln Met Cys Ile Gln Ile Lys Glu Val Gly Asp		1200
	1205	1210
Arg Val Asn Tyr Ile Lys Arg Ser Leu Gln Ser Leu Asp Ser Gln Ile		1215
	1220	1225
Gly His Leu Gln Asp Leu Ser Ala Leu Thr Val Asp Thr Leu Lys Thr		1230
	1235	1240
Leu Thr Ala Gln Lys Ala Ser Glu Ala Ser Lys Val His Asn Glu Ile		1245
	1250	1255
Thr Arg Glu Leu Ser Ile Ser Lys His Leu Ala Gln Asn Leu Ile Asp		1260
1265	1270	1275
Asp Gly Pro Val Arg Pro Ser Val Trp Lys Lys His Gly Val Val Asn		1280
	1285	1290
Thr Leu Ser Ser Ser Leu Pro Gln Gly Asp Leu Glu Ser Asn Asn Pro		1295
	1300	1305
Phe His Cys Asn Ile Leu Met Lys Asp Asp Lys Asp Pro Gln Cys Asn		1310
	1315	1320
Ile Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu Phe Asn		1325
	1330	1335
Phe Pro Glu Ala Gly Ser Ser Ser Gly Ala Leu Phe Pro Ser Ala Val		1340
1345	1350	1355
Ser Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu Leu Lys		1360
	1365	1370
Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser Ile Pro		1375
	1380	1385
His Leu Ser Ser Pro Pro Thr Lys Phe Phe Val Ser Thr Pro Ser Gln		1390
	1395	1400
Pro Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln Glu Thr		1405
	1410	1415
Val Cys Ser Lys Ala Thr Glu Gly Asp Asn Thr Glu Phe Gly Ala Phe		1420
1425	1430	1435
Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser		1440
	1445	1450
Asn Lys Ile Lys Ile Leu Ser Glu Gln Asn Asp Val Arg Asn Val		1455
	1460	1465
Ile Met Glu Tyr Thr Glu Met Pro Lys Tyr Glu Asn Asn Asn Thr Ser		1470
	1475	1480
Glu Asn Thr Leu Lys Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys		1485
	1490	1495
His Arg Thr Ser Ile Pro Val His Ser Lys Gln Ala Glu Lys Ile Ser		1500
1505	1510	1515
Arg Arg Pro Ser Thr Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala		1520
	1525	1530
Leu Ile Pro Asp Trp Leu Gln Asp Arg Pro Ser Asn Arg Glu Met Pro		1535
	1540	1545
Ser Glu Glu Gly Thr Leu Asn Gly Leu Thr Ser Pro Phe Lys Pro Ala		1550
	1555	1560
Met Asp Thr Asn Tyr Tyr Tyr Ser Ala Val Glu Arg Asn Asn Leu Met		1565
	1570	1575
Arg Leu Ser Gln Ser Ile Pro Phe Thr Pro Val Pro Pro Arg Gly Glu		1580
1585	1590	1595
Pro Val Thr Val Tyr Arg Leu Glu Glu Ser Ser Pro Asn Ile Leu Asn		1600
	1605	1610
Asn Ser Met Ser Ser Trp Ser Gln Leu Gly Leu Cys Ala Lys Ile Glu		1615
	1620	1625
Phe Leu Ser Lys Glu Glu Met Gly Gly Gly Leu Arg Arg Ala Val Lys		1630
	1635	1640
Val Gln Cys Thr Trp Ser Glu His Asp Ile Leu Lys Ser Gly His Leu		1645
	1650	1655
		1660

Tyr Ile Ile Lys Ser Phe Leu Pro Glu Val Val Asn Thr Trp Ser Ser
 1665 1670 1675 1680
 Ile Tyr Lys Glu Asp Thr Val Leu His Leu Cys Leu Arg Glu Ile Gln
 1685 1690 1695
 Gln Gln Arg Ala Ala Gln Lys Leu Thr Phe Ala Phe Asn Gln Met Lys
 1700 1705 1710
 Pro Lys Ser Ile Pro Tyr Ser Pro Arg Phe Leu Glu Val Phe Leu Leu
 1715 1720 1725
 Tyr Cys His Ser Ala Gly Gln Trp Phe Ala Val Glu Glu Cys Met Thr
 1730 1735 1740
 Gly Glu Phe Arg Lys Tyr Asn Asn Asn Asn Gly Asp Glu Ile Ile Pro
 1745 1750 1755 1760
 Thr Asn Thr Leu Glu Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr
 1765 1770 1775
 Glu Tyr Thr Arg Gly Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly
 1780 1785 1790
 Glu Asn Leu Thr Asp Pro Ser Val Ile Lys Ala Glu Glu Lys Arg Ser
 1795 1800 1805
 Cys Asp Met Val Phe Gly Pro Ala Asn Leu Gly Glu Asp Ala Ile Lys
 1810 1815 1820

 Asn Phe Arg Ala Lys His His Cys Asn Ser Cys Cys Arg Lys Leu Lys
 1825 1830 1835 1840
 Leu Pro Asp Leu Lys Arg Asn Asp Tyr Thr Pro Asp Lys Ile Ile Phe
 1845 1850 1855
 Pro Gln Asp Glu Pro Ser Asp Leu Asn Leu Gln Pro Gly Asn Ser Thr
 1860 1865 1870
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 1875 1880 1885

<210> 69

<211> 1696

<212> DNA

<213> Homosapien

<400> 69

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 tgaccgtgac ctgactctgg ctggacgcgt cattgtcaag tgccctacct caggctcggct 600
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<210> 70

<211> 475

<212> PRT

<213> Homosapien

<400> 70

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Met Gln Val Ala Met Asn Gly Lys Ala Arg Lys Glu Ala Val Gln Thr
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Ala Ala Lys Glu Leu Leu Lys Phe Val Asn Arg Ser Pro Ser Pro Phe
20      25      30
His Ala Val Ala Glu Cys Arg Asn Arg Leu Leu Gln Ala Gly Phe Ser
35      40      45
Glu Leu Lys Glu Thr Glu Lys Trp Asn Ile Lys Pro Glu Ser Lys Tyr
50      55      60
Phe Met Thr Arg Asn Ser Ser Thr Ile Ile Ala Phe Ala Val Gly Gly
65      70      75      80
Gln Tyr Val Pro Gly Asn Gly Phe Ser Leu Ile Gly Ala His Thr Asp
85      90      95
Ser Pro Cys Leu Arg Val Lys Arg Arg Ser Arg Arg Ser Gln Val Gly
100     105     110
Phe Gln Gln Val Gly Val Glu Thr Tyr Gly Gly Gly Ile Trp Ser Thr
115     120     125
Trp Phe Asp Arg Asp Leu Thr Leu Ala Gly Arg Val Ile Val Lys Cys
130     135     140
Pro Thr Ser Gly Arg Leu Glu Gln Gln Leu Val His Val Glu Arg Pro
145     150     155     160
Ile Leu Arg Ile Pro His Leu Ala Ile His Leu Gln Arg Asn Ile Asn
165     170     175
Glu Asn Phe Gly Pro Asn Thr Glu Met His Leu Val Pro Ile Leu Ala
180     185     190
Thr Ala Ile Gln Glu Glu Leu Glu Lys Gly Thr Pro Glu Pro Gly Pro
195     200     205
Leu Asn Ala Val Asp Glu Arg His His Ser Val Leu Met Ser Leu Leu
210     215     220
Cys Ala His Leu Gly Leu Ser Pro Lys Asp Ile Val Glu Met Glu Leu
225     230     235     240
Cys Leu Ala Asp Thr Gln Pro Ala Val Leu Gly Gly Ala Tyr Asp Glu
245     250     255
Phe Ile Phe Ala Pro Arg Leu Asp Asn Leu His Ser Cys Phe Cys Ala
260     265     270
Leu Gln Ala Leu Ile Asp Ser Cys Ala Gly Pro Gly Ser Leu Ala Thr
275     280     285
Glu Pro His Val Arg Met Val Thr Leu Tyr Asp Asn Glu Glu Val Gly
290     295     300
Ser Glu Ser Ala Gln Gly Ala Gln Ser Leu Leu Thr Glu Leu Val Leu
305     310     315     320
Arg Arg Ile Ser Ala Ser Cys Gln His Pro Thr Ala Phe Glu Glu Ala
325     330     335
Ile Pro Lys Ser Phe Met Ile Ser Ala Asp Met Ala His Ala Val His
340     345     350
Pro Asn Tyr Leu Asp Lys His Glu Glu Asn His Arg Pro Leu Phe His
355     360     365
Lys Gly Pro Val Ile Lys Val Asn Ser Lys Gln Arg Tyr Ala Ser Asn
370     375     380
Ala Val Ser Glu Ala Leu Ile Arg Glu Val Ala Asn Lys Val Lys Val

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385		390		395		400									
Pro	Leu	Gln	Asp	Leu	Met	Val	Arg	Asn	Asp	Thr	Pro	Cys	Gly	Thr	Thr
		405						410						415	
Ile	Gly	Pro	Ile	Leu	Ala	Ser	Arg	Leu	Gly	Leu	Arg	Val	Leu	Asp	Leu
		420						425					430		
Gly	Ser	Pro	Gln	Leu	Ala	Met	His	Ser	Ile	Arg	Glu	Met	Ala	Cys	Thr
		435					440					445			
Thr	Gly	Val	Leu	Gln	Thr	Leu	Thr	Leu	Phe	Lys	Gly	Phe	Phe	Glu	Leu
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Phe	Pro	Ser	Leu	Ser	His	Asn	Leu	Leu	Val	Asp					
465					470					475					

<210> 71
 <211> 2327
 <212> DNA
 <213> Homosapien

<400> 71

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cttcactcac	cactttccct	ctctcgctgt	gttcccaaat	gtgccacttt	tctgttggct	180
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acccatccag	cctgcgctcg	acccaagcag	aagtaaatca	agcagcagca	acaatagcag	2160
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<210> 72
 <211> 378

<212> PRT

<213> Homosapien

<400> 72

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 20           25           30
Lys Glu Ala Ser Glu Gly Ser Thr Leu Thr Thr Val Leu Phe Leu Val
 35           40           45
Ile Cys Ser Phe Ile Val Leu Glu Asn Leu Met Val Leu Ile Ala Ile
 50           55           60
Trp Lys Asn Asn Lys Phe His Asn Arg Met Tyr Phe Phe Ile Gly Asn
 65           70           75           80
Leu Ala Leu Cys Asp Leu Leu Ala Gly Ile Ala Tyr Lys Val Asn Ile
 85           90           95
Leu Met Ser Gly Lys Lys Thr Phe Ser Leu Ser Pro Thr Val Trp Phe
100          105          110
Leu Arg Glu Gly Ser Met Phe Val Ala Leu Gly Ala Ser Thr Cys Ser

          115          120          125
Leu Leu Ala Ile Ala Ile Glu Arg His Leu Thr Met Ile Lys Met Arg
130          135          140
Pro Tyr Asp Ala Asn Lys Arg His Arg Val Phe Leu Leu Ile Gly Met
145          150          155          160
Cys Trp Leu Ile Ala Phe Thr Leu Gly Ala Leu Pro Ile Leu Gly Trp
165          170          175
Asn Cys Leu His Asn Leu Pro Asp Cys Ser Thr Ile Leu Pro Leu Tyr
180          185          190
Ser Lys Lys Tyr Ile Ala Phe Cys Ile Ser Ile Phe Thr Ala Ile Leu
195          200          205
Val Thr Ile Val Ile Leu Tyr Ala Arg Ile Tyr Phe Leu Val Lys Ser
210          215          220
Ser Ser Arg Lys Val Ala Asn His Asn Asn Ser Glu Arg Ser Met Ala
225          230          235          240
Leu Leu Arg Thr Val Val Ile Val Val Ser Val Phe Ile Ala Cys Trp
245          250          255
Ser Pro Leu Phe Ile Leu Phe Leu Ile Asp Val Ala Cys Arg Val Gln
260          265          270
Ala Cys Pro Ile Leu Phe Lys Ala Gln Trp Phe Ile Val Leu Ala Val
275          280          285
Leu Asn Ser Ala Met Asn Pro Val Ile Tyr Thr Leu Ala Ser Lys Glu
290          295          300
Met Arg Arg Ala Phe Phe Arg Leu Val Cys Asn Cys Leu Val Arg Gly
305          310          315          320
Arg Gly Ala Arg Ala Ser Pro Ile Gln Pro Ala Leu Asp Pro Ser Arg
325          330          335
Ser Lys Ser Ser Ser Ser Asn Asn Ser Ser His Ser Pro Lys Val Lys
340          345          350
Glu Asp Leu Pro His Thr Asp Pro Ser Ser Cys Ile Met Asp Lys Asn
355          360          365
Ala Ala Leu Gln Asn Gly Ile Phe Cys Asn
370          375

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<210> 73

<211> 1576

<212> DNA

<213> Homosapien

<400> 73

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<210> 74

<211> 364

<212> PRT

<213> Homosapien

<400> 74

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Phe Tyr Asn Arg Ser Gly Lys His Leu Ala Thr Glu Trp Asn Thr Val
35        40        45
Ser Lys Leu Val Met Gly Leu Gly Ile Thr Val Cys Ile Phe Ile Met
50        55        60
Leu Ala Asn Leu Leu Val Met Val Ala Ile Tyr Val Asn Arg Arg Phe
65        70        75        80
His Phe Pro Ile Tyr Tyr Leu Met Ala Asn Leu Ala Ala Ala Asp Phe
85        90        95
Phe Ala Gly Leu Ala Tyr Phe Tyr Leu Met Phe Asn Thr Gly Pro Asn
100       105       110
Thr Arg Arg Leu Thr Val Ser Thr Trp Leu Leu Arg Gln Gly Leu Ile
115       120       125
Asp Thr Ser Leu Thr Ala Ser Val Ala Asn Leu Leu Ala Ile Ala Ile
130       135       140
Glu Arg His Ile Thr Val Phe Arg Met Gln Leu His Thr Arg Met Ser
145       150       155       160
Asn Arg Arg Val Val Val Val Ile Val Val Ile Trp Thr Met Ala Ile
165       170       175
Val Met Gly Ala Ile Pro Ser Val Gly Trp Asn Cys Ile Cys Asp Ile
180       185       190
Glu Asn Cys Ser Asn Met Ala Pro Leu Tyr Ser Asp Ser Tyr Leu Val
195       200       205
Phe Trp Ala Ile Phe Asn Leu Val Thr Phe Val Val Met Val Val Leu

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210	215	220
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Arg His Ser Ser Gly Pro Arg Arg Asn Arg Asp Thr Met Met Ser Leu		240
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	260	265
Pro Gly Leu Val Leu Leu Leu Leu Asp Val Cys Cys Pro Gln Cys Asp		270
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Val Leu Ala Tyr Glu Lys Phe Phe Leu Leu Leu Ala Glu Phe Asn Ser		285
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Ala Met Asn Pro Ile Ile Tyr Ser Tyr Arg Asp Lys Glu Met Ser Ala		300
305	310	315
Thr Phe Arg Gln Ile Leu Cys Cys Gln Arg Ser Glu Asn Pro Thr Gly		320
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<210> 75

<211> 2192

<212> DNA

<213> Homosapien

<400> 75

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 tccttgga aa aaaaaaaaaa aaaaaaaaaa aa 2192

<210> 76

<211> 647

<212> PRT

<213> Homosapien

<400> 76

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			20					25					30		
Thr	Ser	Gly	Gln	Gly	Ala	Leu	Asp	Gln	Glu	Ala	Leu	Gly	Gly	Leu	Leu
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Asn	Thr	Leu	Ala	Asp	Arg	Val	His	Cys	Thr	Asn	Gly	Pro	Cys	Gly	Lys
	50					55					60				
Cys	Leu	Ser	Val	Glu	Asp	Ala	Leu	Gly	Leu	Gly	Glu	Pro	Glu	Gly	Ser
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Gly	Leu	Pro	Pro	Gly	Pro	Val	Leu	Glu	Ala	Arg	Tyr	Val	Ala	Arg	Leu
				85					90					95	
Ser	Ala	Ala	Ala	Val	Leu	Tyr	Leu	Ser	Asn	Pro	Glu	Gly	Thr	Cys	Glu
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Asp	Thr	Arg	Ala	Gly	Leu	Trp	Ala	Ser	His	Ala	Asp	His	Leu	Leu	Ala
		115					120					125			
Leu	Leu	Glu	Ser	Pro	Lys	Ala	Leu	Thr	Pro	Gly	Leu	Ser	Trp	Leu	Leu
	130					135					140				
Gln	Arg	Met	Gln	Ala	Arg	Ala	Ala	Gly	Gln	Thr	Pro	Lys	Thr	Ala	Cys
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Ser	Ala	Leu	Met	Gln	Arg	Leu	Gly	Val	Gly	Arg	Glu	Ala	His	Ser	Asp
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His	Ser	His	Arg	His	Arg	Gly	Ala	Ser	Ser	Arg	Asp	Pro	Val	Pro	Leu
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Ala	Arg	Asp	Val	Met	Ala	Ala	Tyr	Gly	Leu	Ser	Glu	Gln	Ala	Gly	Val
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			325						330					335	
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Leu	Gly	Leu	His	Thr	His	Ser	Glu	Glu	Gly	Leu	Ser	Pro	Gln	Pro	Thr
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Trp	Arg	Leu	Leu	Ala	Met	Leu	Ala	Gly	Leu	Tyr	Ala	Phe	Phe	Leu	Phe

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Asp	Gly	Pro	Cys	Gly	His	Ser	Ser	His	Ser	His	Gly	Gly	His	Ser	His	
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Pro	His	Glu	Gly	Ser	Arg	Ala	Asp	Leu	Val	Ala	Glu	Glu	Ser	Pro	Glu	
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Phe	Ala	Ala	Leu	Leu	His	Ala	Gly	Leu	Ser	Val	Arg	Gln	Ala	Leu	Leu	
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Leu	Asn	Leu	Ala	Ser	Ala	Leu	Thr	Ala	Phe	Ala	Gly	Leu	Tyr	Val	Ala	
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Leu	Ala	Val	Gly	Val	Ser	Glu	Glu	Ser	Glu	Ala	Trp	Ile	Leu	Ala	Val	
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Ala	Thr	Gly	Leu	Phe	Leu	Tyr	Val	Ala	Leu	Cys	Asp	Met	Leu	Pro	Ala	
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Tyr	Glu	Asp	Asp	Ile	Thr	Phe										
645																

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<210> 77
<211> 2952
<212> DNA
<213> Homosapien
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<400> 77

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<211> 765

<212> PRT

<213> Homosapien

<400> 78

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			20					25					30		
Ile	Val	Leu	Leu	Cys	Phe	Thr	Lys	Phe	Leu	Lys	Ala	Val	Gly	Leu	Phe
			35				40					45			
Glu	Ser	Tyr	Asp	Leu	Leu	Lys	Ala	Val	His	Ile	Val	Gln	Phe	Ile	Phe
			50				55				60				
Ile	Leu	Lys	Leu	Gly	Thr	Ala	Phe	Phe	Met	Val	Leu	Phe	Gln	Lys	Pro
						70				75					80
Phe	Ser	Ser	Gly	Lys	Thr	Ile	Thr	Lys	His	Gln	Trp	Ile	Lys	Ile	Phe
				85				90					95		
Lys	His	Ala	Val	Ala	Gly	Cys	Ile	Ile	Ser	Leu	Leu	Trp	Phe	Phe	Gly
			100					105					110		
Leu	Thr	Leu	Cys	Gly	Pro	Leu	Arg	Thr	Leu	Leu	Leu	Phe	Glu	His	Ser
			115				120					125			
Asp	Ile	Val	Val	Ile	Ser	Leu	Leu	Ser	Val	Leu	Phe	Thr	Ser	Ser	Gly
			130				135				140				
Gly	Gly	Pro	Ala	Lys	Thr	Arg	Gly	Ala	Ala	Phe	Phe	Ile	Ile	Ala	Val
						150				155					160
Ile	Cys	Leu	Leu	Leu	Phe	Asp	Asn	Asp	Asp	Leu	Met	Ala	Lys	Met	Ala
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Glu	His	Pro	Glu	Gly	His	His	Asp	Ser	Ala	Leu	Thr	His	Met	Leu	Tyr
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 210 215 220
 Arg Lys Leu Ser Val Asp Val Gly Gly Ala Lys Arg Leu Gln Ala Leu
 225 230 235 240
 Ser His Leu Val Ser Val Leu Leu Leu Cys Pro Trp Val Ile Val Leu
 245 250 255
 Ser Val Thr Thr Glu Ser Lys Val Glu Ser Trp Phe Ser Leu Ile Met
 260 265 270
 Pro Phe Ala Thr Val Ile Phe Phe Val Met Ile Leu Asp Phe Tyr Val
 275 280 285
 Asp Ser Ile Cys Ser Val Lys Met Glu Val Ser Lys Cys Ala Arg Tyr
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 Gly Ser Phe Pro Ile Phe Ile Ser Ala Leu Leu Phe Gly Asn Phe Trp
 305 310 315 320
 Thr His Pro Ile Thr Asp Gln Leu Arg Ala Met Asn Lys Ala Ala His
 325 330 335
 Gln Glu Ser Thr Glu His Val Leu Ser Gly Gly Val Val Val Ser Ala
 340 345 350
 Ile Phe Phe Ile Leu Ser Ala Asn Ile Leu Ser Ser Pro Ser Lys Arg
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 Gly Gln Lys Gly Thr Leu Ile Gly Tyr Ser Pro Glu Gly Thr Pro Leu
 370 375 380
 Tyr Asn Phe Met Gly Asp Ala Phe Gln His Ser Ser Gln Ser Ile Pro
 385 390 395 400
 Arg Phe Ile Lys Glu Ser Leu Lys Gln Ile Leu Glu Glu Ser Asp Ser
 405 410 415
 Arg Gln Ile Phe Tyr Phe Leu Cys Leu Asn Leu Leu Phe Thr Phe Val
 420 425 430
 Glu Leu Phe Tyr Gly Val Leu Thr Asn Ser Leu Gly Leu Ile Ser Asp
 435 440 445
 Gly Phe His Met Leu Phe Asp Cys Ser Ala Leu Val Met Gly Leu Phe
 450 455 460
 Ala Ala Leu Met Ser Arg Trp Lys Ala Thr Arg Ile Phe Ser Tyr Gly
 465 470 475 480
 Tyr Gly Arg Ile Glu Ile Leu Ser Gly Phe Ile Asn Gly Leu Phe Leu
 485 490 495
 Ile Val Ile Ala Phe Phe Val Phe Met Glu Ser Val Ala Arg Leu Ile
 500 505 510
 Asp Pro Pro Glu Leu Asp Thr His Met Leu Thr Pro Val Ser Val Gly
 515 520 525
 Gly Leu Ile Val Asn Leu Ile Gly Ile Cys Ala Phe Ser His Ala His
 530 535 540
 Ser His Ala His Gly Ala Ser Gln Gly Ser Cys His Ser Ser Asp His
 545 550 555 560
 Ser His Ser His His Met His Gly His Ser Asp His Gly His Gly His
 565 570 575
 Ser His Gly Ser Ala Gly Gly Gly Met Asn Ala Asn Met Arg Gly Val
 580 585 590
 Phe Leu His Val Leu Ala Asp Thr Leu Gly Ser Ile Gly Val Ile Val
 595 600 605
 Ser Thr Val Leu Ile Glu Gln Phe Gly Trp Phe Ile Ala Asp Pro Leu
 610 615 620
 Cys Ser Leu Phe Ile Ala Ile Leu Ile Phe Leu Ser Val Val Pro Leu
 625 630 635 640
 Ile Lys Asp Ala Cys Gln Val Leu Leu Leu Arg Leu Pro Pro Glu Tyr
 645 650 655
 Glu Lys Glu Leu His Ile Ala Leu Glu Lys Ile Gln Lys Ile Glu Gly
 660 665 670

Leu	Ile	Ser	Tyr	Arg	Asp	Pro	His	Phe	Trp	Arg	His	Ser	Ala	Ser	Ile
	675						680					685			
Val	Ala	Gly	Thr	Ile	His	Ile	Gln	Val	Thr	Ser	Asp	Val	Leu	Glu	Gln
	690						695				700				
Arg	Ile	Val	Gln	Gln	Val	Thr	Gly	Ile	Leu	Lys	Asp	Ala	Gly	Val	Asn
	705					710				715					720
Asn	Leu	Thr	Ile	Gln	Val	Glu	Lys	Glu	Ala	Tyr	Phe	Gln	His	Met	Ser
				725					730					735	
Gly	Leu	Ser	Thr	Gly	Phe	His	Asp	Val	Leu	Ala	Met	Thr	Lys	Gln	Met
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<210> 79
 <211> 2074
 <212> DNA
 <213> Homosapien

<400> 79

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aatgagtgca	aagcgcggag	agccgcgtcg	gcggccacgg	cagcgccac	ggccactccc	240
gccgcgcagg	agtcgggcac	catcccaaag	aagcggcaag	aagttatgaa	atggaatgga	300
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<210> 80
 <211> 658
 <212> PRT
 <213> Homosapien

<400> 80

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Arg Ala Gly Arg Arg Leu Arg Val Leu Ser Gly His Leu Leu Gly Arg
          35          40          45
Pro Arg Glu Ala Leu Ser Thr Asn Glu Cys Lys Ala Arg Arg Ala Ala
          50          55          60
Ser Ala Ala Thr Ala Ala Pro Thr Ala Thr Pro Ala Ala Gln Glu Ser
65          70          75          80
Gly Thr Ile Pro Lys Lys Arg Gln Glu Val Met Lys Trp Asn Gly Trp
          85          90          95
Gly Tyr Asn Asp Ser Lys Phe Ile Phe Asn Lys Lys Gly Gln Ile Glu
          100          105          110
Leu Thr Gly Lys Arg Tyr Pro Leu Ser Gly Met Gly Leu Pro Thr Phe
          115          120          125
Lys Glu Trp Ile Gln Asn Thr Leu Gly Val Asn Val Glu His Lys Thr
          130          135          140
Thr Ser Lys Ala Ser Leu Asn Pro Ser Asp Thr Pro Pro Ser Val Val
145          150          155          160
Asn Glu Asp Phe Leu His Asp Leu Lys Glu Thr Asn Ile Ser Tyr Ser
          165          170          175
Gln Glu Ala Asp Asp Arg Val Phe Arg Ala His Gly His Cys Leu His
          180          185          190
Glu Ile Phe Leu Leu Arg Glu Gly Met Phe Glu Arg Ile Pro Asp Ile
          195          200          205
Val Leu Trp Pro Thr Cys His Asp Asp Val Val Lys Ile Val Asn Leu
          210          215          220
Ala Cys Lys Tyr Asn Leu Cys Ile Ile Pro Ile Gly Gly Gly Thr Ser
225          230          235          240
Val Ser Tyr Gly Leu Met Cys Pro Ala Asp Glu Thr Arg Thr Ile Ile
          245          250          255
Ser Leu Asp Thr Ser Gln Met Asn Arg Ile Leu Trp Val Asp Glu Asn
          260          265          270
Asn Leu Thr Ala His Val Glu Ala Gly Ile Thr Gly Gln Glu Leu Glu
          275          280          285
Arg Gln Leu Lys Glu Ser Gly Tyr Cys Thr Gly His Glu Pro Asp Ser
          290          295          300
Leu Glu Phe Ser Thr Val Gly Gly Trp Val Ser Thr Arg Ala Ser Gly
305          310          315          320
Met Lys Lys Asn Ile Tyr Gly Asn Ile Glu Asp Leu Val Val His Ile
          325          330          335
Lys Met Val Thr Pro Arg Gly Ile Ile Glu Lys Ser Cys Gln Gly Pro
          340          345          350
Arg Met Ser Thr Gly Pro Asp Ile His His Phe Ile Met Gly Ser Glu
          355          360          365
Gly Thr Leu Gly Val Ile Thr Glu Ala Thr Ile Lys Ile Arg Pro Val
          370          375          380
Pro Glu Tyr Gln Lys Tyr Gly Ser Val Ala Phe Pro Asn Phe Glu Gln
385          390          395          400
Gly Val Ala Cys Leu Arg Glu Ile Ala Lys Gln Arg Cys Ala Pro Ala
          405          410          415
Ser Ile Arg Leu Met Asp Asn Lys Gln Phe Gln Phe Gly His Ala Leu
          420          425          430
Lys Pro Gln Val Ser Ser Ile Phe Thr Ser Phe Leu Asp Gly Leu Lys
          435          440          445
Lys Phe Tyr Ile Thr Lys Phe Lys Gly Phe Asp Pro Asn Gln Leu Ser
          450          455          460
Val Ala Thr Leu Leu Phe Glu Gly Asp Arg Glu Lys Val Leu Gln His
465          470          475          480

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Glu Lys Gln Val Tyr Asp Ile Ala Ala Lys Phe Gly Gly Leu Ala Ala
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 Gly Glu Asp Asn Gly Gln Arg Gly Tyr Leu Leu Thr Tyr Val Ile Ala
 500 505 510
 Tyr Ile Arg Asp Leu Ala Leu Glu Tyr Tyr Val Leu Gly Glu Ser Phe
 515 520 525
 Glu Thr Ser Ala Pro Trp Asp Arg Val Val Asp Leu Cys Arg Asn Val
 530 535 540
 Lys Glu Arg Ile Thr Arg Glu Cys Lys Glu Lys Gly Val Gln Phe Ala
 545 550 555 560
 Pro Phe Ser Thr Cys Arg Val Thr Gln Thr Tyr Asp Ala Gly Ala Cys
 565 570 575
 Ile Tyr Phe Tyr Phe Ala Phe Asn Tyr Arg Gly Ile Ser Asp Pro Leu
 580 585 590
 Thr Val Phe Glu Gln Thr Glu Ala Ala Ala Arg Glu Glu Ile Leu Ala
 595 600 605
 Asn Gly Gly Ser Leu Ser His His His Gly Val Gly Lys Leu Arg Lys
 610 615 620
 Gln Trp Leu Lys Glu Ser Ile Ser Asp Val Gly Phe Gly Met Leu Lys
 625 630 635 640
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 645 650 655
 Leu Leu

<210> 81
 <211> 1753
 <212> DNA
 <213> Homosapien

<400> 81
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 ctttctaaga actaatataa ttgctacctt aaaaaggaaa aatgaacag cacatgtatt 540
 gaagaacagc atgacctgga tctactattg tttccattg tttacatctt tgtgattata 600
 gtcagcattc cagccaatat tggatctctg tgtgtgtctt tcttgcaacc caagaaggaa 660
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1753

<210> 82

<211> 337

<212> PRT

<213> Homosapien

<400> 82

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 Ile Gly Ser Leu Cys Val Ser Phe Leu Gln Pro Lys Lys Glu Ser Glu
 35 40 45
 Leu Gly Ile Tyr Leu Phe Ser Leu Ser Leu Ser Asp Leu Leu Tyr Ala
 50 55 60
 Leu Thr Leu Pro Leu Trp Ile Asp Tyr Thr Trp Asn Lys Asp Asn Trp
 65 70 75 80
 Thr Phe Ser Pro Ala Leu Cys Lys Gly Ser Ala Phe Leu Met Tyr Met
 85 90 95
 Lys Phe Tyr Ser Ser Thr Ala Phe Leu Thr Cys Ile Ala Val Asp Arg
 100 105 110
 Tyr Leu Ala Val Val Tyr Pro Leu Lys Phe Phe Phe Leu Arg Thr Arg
 115 120 125
 Arg Ile Ala Leu Met Val Ser Leu Ser Ile Trp Ile Leu Glu Thr Ile
 130 135 140
 Phe Asn Ala Val Met Leu Trp Glu Asp Glu Thr Val Val Glu Tyr Cys
 145 150 155 160
 Asp Ala Glu Lys Ser Asn Phe Thr Leu Cys Tyr Asp Lys Tyr Pro Leu
 165 170 175
 Glu Lys Trp Gln Ile Asn Leu Asn Leu Phe Arg Thr Cys Thr Gly Tyr
 180 185 190
 Ala Ile Pro Leu Val Thr Ile Leu Ile Cys Asn Arg Lys Val Tyr Gln
 195 200 205
 Ala Val Arg His Asn Lys Ala Thr Glu Asn Lys Glu Lys Lys Arg Ile
 210 215 220
 Ile Lys Leu Leu Val Ser Ile Thr Val Thr Phe Val Leu Cys Phe Thr
 225 230 235 240
 Pro Phe His Val Met Leu Leu Ile Arg Cys Ile Leu Glu His Ala Val
 245 250 255
 Asn Phe Glu Asp His Ser Asn Ser Gly Lys Arg Thr Tyr Thr Met Tyr
 260 265 270
 Arg Ile Thr Val Ala Leu Thr Ser Leu Asn Cys Val Ala Asp Pro Ile
 275 280 285
 Leu Tyr Cys Phe Val Thr Glu Thr Gly Arg Tyr Asp Met Trp Asn Ile
 290 295 300
 Leu Lys Phe Cys Thr Gly Arg Cys Asn Thr Ser Gln Arg Gln Arg Lys
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 Arg Ile Leu Ser Val Ser Thr Lys Asp Thr Met Glu Leu Glu Val Leu
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<210> 83

<211> 1053

<212> DNA

<213> Homosapien

<400> 83

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<210> 84

<211> 349

<212> PRT

<213> Homosapien

<400> 84

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          20          25          30
Asn Phe Val Thr Leu Val Val Phe Gly Leu Ile Phe Ala Leu Gly Val
          35          40          45
Leu Gly Asn Ser Leu Val Ile Thr Val Leu Ala Arg Ser Lys Pro Gly
          50          55          60
Lys Pro Arg Ser Thr Thr Asn Leu Phe Ile Leu Asn Leu Ser Ile Ala
          65          70          75          80
Asp Leu Ala Tyr Leu Leu Phe Cys Ile Pro Phe Gln Ala Thr Val Tyr
          85          90          95
Ala Leu Pro Thr Trp Val Leu Gly Ala Phe Ile Cys Lys Phe Ile His
          100          105          110
Tyr Phe Phe Thr Val Ser Met Leu Val Ser Ile Phe Thr Leu Ala Ala
          115          120          125
Met Ser Val Asp Arg Tyr Val Ala Ile Val His Ser Arg Arg Ser Ser
          130          135          140
Ser Leu Arg Val Ser Arg Asn Ala Leu Leu Gly Val Gly Cys Ile Trp
          145          150          155          160
Ala Leu Ser Ile Ala Met Ala Ser Pro Val Ala Tyr His Gln Gly Leu
          165          170          175
Phe His Pro Arg Ala Ser Asn Gln Thr Phe Cys Trp Glu Gln Trp Pro
          180          185          190
Asp Pro Arg His Lys Lys Ala Tyr Val Val Cys Thr Phe Val Phe Gly
          195          200          205
Tyr Leu Leu Pro Leu Leu Leu Ile Cys Phe Cys Tyr Ala Lys Val Leu
          210          215          220
Asn His Leu His Lys Lys Leu Lys Asn Met Ser Lys Lys Ser Glu Ala
          225          230          235          240
Ser Lys Lys Lys Thr Ala Gln Thr Val Leu Val Val Val Val Phe
          245          250          255
Gly Ile Ser Trp Leu Pro His His Ile Ile His Leu Trp Ala Glu Phe
          260          265          270
Gly Val Phe Pro Leu Thr Pro Ala Ser Phe Leu Phe Arg Ile Thr Ala
          275          280          285
His Cys Leu Ala Tyr Ser Asn Ser Ser Val Asn Pro Ile Ile Tyr Ala

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290		295		300
Phe Leu Ser Glu Asn	Phe Arg Lys Ala Tyr Lys	Gln Val Phe Lys Cys		
305	310	315	320	
His Ile Arg Lys Asp	Ser His Leu Ser Asp Thr	Lys Glu Asn Lys Ser		
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Arg Ile Asp Thr Pro	Pro Ser Thr Asn Cys Thr	His Val		
	340	345		

<210> 85
 <211> 3321
 <212> DNA
 <213> Homosapien

<400> 85

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<210> 86

<211> 908

<212> PRT

<213> Homosapien

<400> 86

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Ser Gln Glu Tyr Ala His Ser Ile Arg Val Asp Gly Asp Ile Ile Leu
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Gly Glu Leu Lys Lys Glu Lys Gly Ile His Arg Leu Glu Ala Met Leu
65          70          75          80
Tyr Ala Ile Asp Gln Ile Asn Lys Asp Pro Asp Leu Leu Ser Asn Ile
          85          90          95
Thr Leu Gly Val Arg Ile Leu Asp Thr Cys Ser Arg Asp Thr Tyr Ala
          100          105          110
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Asp Lys Ile Ser Gly Val Ile Gly Ala Ala Ala Ser Ser Val Ser Ile
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Met Val Ala Asn Ile Leu Arg Leu Phe Lys Ile Pro Gln Ile Ser Tyr
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Ala Ser Thr Ala Pro Glu Leu Ser Asp Asn Thr Arg Tyr Asp Phe Phe
          180          185          190
Ser Arg Val Val Pro Pro Asp Ser Tyr Gln Ala Gln Ala Met Val Asp
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Ile Val Thr Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu Ala Ser Glu
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Gly Asn Tyr Gly Glu Ser Gly Val Glu Ala Phe Thr Gln Ile Ser Arg
225          230          235          240
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Pro Asn Ala Arg Ala Val Ile Met Phe Ala Asn Glu Asp Asp Ile Arg
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Arg Ile Leu Glu Ala Ala Lys Lys Leu Asn Gln Ser Gly His Phe Leu
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 820 825 830
 Leu Tyr Met Pro Lys Val Tyr Ile Ile Ile Phe His Pro Glu Gln Asn

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Val Lys Ser Glu Leu Cys Glu Ser Leu Glu Thr	Asn Thr Ser Ser Thr	
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 <211> 2896
 <212> DNA
 <213> Homosapien

<400> 87

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<211> 379

<212> PRT

<213> Homosapien

<400> 88

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Ala	Ser	Pro	Ser	Gly	Leu	Arg	Asp	Ser	Thr	Val	Arg	Tyr	Gly	Asp	Pro
		340					345						350		
Glu	Lys	Leu	Lys	Leu	Glu	Glu	Ser	Leu	Arg	Glu	Gln	Ala	Glu	Lys	Glu
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 <212> DNA
 <213> Homosapien

<400> 89
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 <212> PRT
 <213> Homosapien

<400> 90
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 His Lys Gly Pro Pro Val Phe Thr Gln Glu Glu Arg Tyr Lys Met Val
 65 70 75 80
 Gln Ala Ile Lys Trp Val Asp Glu Val Val Pro Ala Ala Pro Tyr Val
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<210> 91

<211> 3165

<212> DNA

<213> Homosapien

<400> 91

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```

<210> 92

<211> 720

<212> PRT

<213> Homosapien

<400> 92

```

Met Asn Asn His Val Ser Ser Lys Pro Ser Thr Met Lys Leu Lys His
  1          5          10          15
Thr Ile Asn Pro Ile Leu Leu Tyr Phe Ile His Phe Leu Ile Ser Leu
          20          25          30
Tyr Thr Ile Leu Thr Tyr Ile Pro Phe Tyr Phe Phe Ser Glu Ser Arg
          35          40          45
Gln Glu Lys Ser Asn Arg Ile Lys Ala Lys Pro Val Asn Ser Lys Pro
          50          55          60
Asp Ser Ala Tyr Arg Ser Val Asn Ser Leu Asp Gly Leu Ala Ser Val
          65          70          75          80
Leu Tyr Pro Gly Cys Asp Thr Leu Asp Lys Val Phe Thr Tyr Ala Lys
          85          90          95
Asn Lys Phe Lys Asn Lys Arg Leu Leu Gly Thr Arg Glu Val Leu Asn
          100          105          110
Glu Glu Asp Glu Val Gln Pro Asn Gly Lys Ile Phe Lys Lys Val Ile
          115          120          125
Leu Gly Gln Tyr Asn Trp Leu Ser Tyr Glu Asp Val Phe Val Arg Ala
          130          135          140
Phe Asn Phe Gly Asn Gly Leu Gln Met Leu Gly Gln Lys Pro Lys Thr
          145          150          155          160

```

Asn Ile Ala Ile Phe Cys Glu Thr Arg Ala Glu Trp Met Ile Ala Ala
 165 170 175
 Gln Ala Cys Phe Met Tyr Asn Phe Gln Leu Val Thr Leu Tyr Ala Thr
 180 185 190
 Leu Gly Gly Pro Ala Ile Val His Ala Leu Asn Glu Thr Glu Val Thr
 195 200 205
 Asn Ile Ile Thr Ser Lys Glu Leu Leu Gln Thr Lys Leu Lys Asp Ile
 210 215 220
 Val Ser Leu Val Pro Arg Leu Arg His Ile Ile Thr Val Asp Gly Lys
 225 230 235 240
 Pro Pro Thr Trp Ser Asp Phe Pro Lys Gly Ile Ile Val His Thr Met
 245 250 255
 Ala Ala Val Glu Ala Leu Gly Ala Lys Ala Ser Met Glu Asn Gln Pro
 260 265 270
 His Ser Lys Pro Leu Pro Ser Asp Ile Ala Val Ile Met Tyr Thr Ser
 275 280 285
 Gly Ser Thr Gly Leu Pro Lys Gly Val Met Ile Ser His Ser Asn Ile
 290 295 300
 Ile Ala Gly Ile Thr Gly Met Ala Glu Arg Ile Pro Glu Leu Gly Glu
 305 310 315 320
 Glu Asp Val Tyr Ile Gly Tyr Leu Pro Leu Ala His Val Leu Glu Leu
 325 330 335
 Ser Ala Glu Leu Val Cys Leu Ser His Gly Cys Arg Ile Gly Tyr Ser
 340 345 350
 Ser Pro Gln Thr Leu Ala Asp Gln Ser Ser Lys Ile Lys Lys Gly Ser
 355 360 365
 Lys Gly Asp Thr Ser Met Leu Lys Pro Thr Leu Met Ala Ala Val Pro
 370 375 380
 Glu Ile Met Asp Arg Ile Tyr Lys Asn Val Met Asn Lys Val Ser Glu
 385 390 395 400
 Met Ser Ser Phe Gln Arg Asn Leu Phe Ile Leu Ala Tyr Asn Tyr Lys
 405 410 415
 Met Glu Gln Ile Ser Lys Gly Arg Asn Thr Pro Leu Cys Asp Ser Phe
 420 425 430
 Val Phe Arg Lys Val Arg Ser Leu Leu Gly Gly Asn Ile Arg Leu Leu
 435 440 445
 Leu Cys Gly Gly Ala Pro Leu Ser Ala Thr Thr Gln Arg Phe Met Asn
 450 455 460
 Ile Cys Phe Cys Cys Pro Val Gly Gln Gly Tyr Gly Leu Thr Glu Ser
 465 470 475 480
 Ala Gly Ala Gly Thr Ile Ser Glu Val Trp Asp Tyr Asn Thr Gly Arg
 485 490 495
 Val Gly Ala Pro Leu Val Cys Cys Glu Ile Lys Leu Lys Asn Trp Glu
 500 505 510
 Glu Gly Gly Tyr Phe Asn Thr Asp Lys Pro His Pro Arg Gly Glu Ile
 515 520 525
 Leu Ile Gly Gly Gln Ser Val Thr Met Gly Tyr Tyr Lys Asn Glu Ala
 530 535 540
 Lys Thr Lys Ala Asp Phe Ser Glu Asp Glu Asn Gly Gln Arg Trp Leu
 545 550 555 560
 Cys Thr Gly Asp Ile Gly Glu Phe Glu Pro Asp Gly Cys Leu Lys Ile
 565 570 575
 Ile Asp Arg Lys Lys Asp Leu Val Lys Leu Gln Ala Gly Glu Tyr Val
 580 585 590
 Ser Leu Gly Lys Val Glu Ala Ala Leu Lys Asn Leu Pro Leu Val Asp
 595 600 605
 Asn Ile Cys Ala Tyr Ala Asn Ser Tyr His Ser Tyr Val Ile Gly Phe
 610 615 620
 Val Val Pro Asn Gln Lys Glu Leu Thr Glu Leu Ala Arg Lys Lys Gly
 625 630 635 640
 Leu Lys Gly Thr Trp Glu Glu Leu Cys Asn Ser Cys Glu Met Glu Asn

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<210> 93
<211> 1124
<212> DNA
<213> Homosapien
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aatccttgag	gaagagcctc	ccagcatcct	taaaggttta	tggaactgtc	tttcacataa	240
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aacttgggtt	tcctgtctat	tctcatgtag	actacagcaa	tgaagctatg	caaaaaatga	960
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tgtgatgcca	atcctgaaca	taagacagtg	ttgggcaggt	ctgggcgtat	aatttgagga	1080
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<210> 94
<211> 296
<212> PRT
<213> Homosapien
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Met	Met	Leu	Pro	Leu	Gln	Gly	Ala	Gln	Met	Leu	Gln	Met	Leu	Glu	Lys
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Ser	Leu	Arg	Lys	Ser	Leu	Pro	Ala	Ser	Leu	Lys	Val	Tyr	Gly	Thr	Val
			20					25					30		
Phe	His	Ile	Asn	His	Gly	Asn	Pro	Phe	Asn	Leu	Lys	Ala	Val	Val	Asp
		35					40					45			
Lys	Trp	Pro	Asp	Phe	Asn	Thr	Val	Val	Val	Cys	Pro	Gln	Glu	Gln	Asp
	50					55					60				
Met	Thr	Asp	Asp	Leu	Asp	His	Tyr	Thr	Asn	Thr	Tyr	Gln	Ile	Tyr	Ser
65					70					75					80
Lys	Asp	Pro	Gln	Asn	Cys	Gln	Glu	Phe	Leu	Gly	Ser	Pro	Glu	Leu	Ile
				85					90					95	
Asn	Trp	Lys	Gln	His	Leu	Gln	Ile	Gln	Ser	Ser	Gln	Pro	Ser	Leu	Asn
			100					105					110		
Glu	Ala	Ile	Gln	Asn	Leu	Ala	Ala	Ile	Lys	Ser	Phe	Lys	Val	Lys	Gln
		115					120					125			
Thr	Gln	Arg	Ile	Leu	Tyr	Met	Ala	Ala	Glu	Thr	Ala	Lys	Glu	Leu	Thr

130	135	140
Pro Phe Leu Leu Lys Ser Lys Ile Leu Ser Pro Ser Gly Gly Lys Pro		
145	150	155
Lys Ala Ile Asn Gln Glu Met Phe Lys Leu Ser Ser Met Asp Val Thr		160
	165	170
His Ala His Leu Val Asn Lys Phe Trp His Phe Gly Gly Asn Glu Arg		175
	180	185
Ser Gln Arg Phe Ile Glu Arg Cys Ile Gln Thr Phe Pro Thr Cys Cys		190
	195	200
Leu Leu Gly Pro Glu Gly Thr Pro Val Cys Trp Asp Leu Met Asp Gln		205
	210	215
Thr Gly Glu Met Arg Met Ala Gly Thr Phe Ala Glu Tyr Arg Leu His		220
225	230	235
Gly Leu Val Thr Tyr Val Ile Tyr Ser His Ala Gln Lys Leu Gly Lys		240
	245	250
Leu Gly Phe Pro Val Tyr Ser His Val Asp Tyr Ser Asn Glu Ala Met		255
	260	265
Gln Lys Met Ser Tyr Thr Leu Gln His Val Pro Ile Pro Arg Ser Trp		270
	275	280
Asn Gln Trp Asn Cys Val Pro Leu		285
	290	295

<210> 95
 <211> 3040
 <212> DNA
 <213> Homosapien

<220>
 <221> misc_feature
 <222> (1)...(3040)
 <223> n = A,T,C or G

<400> 95

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<210> 96

<211> 902

<212> PRT

<213> Homosapien

<400> 96

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Cys His Leu Arg Lys Glu Gly His Glu Val Val Gly Val Phe Thr Val
  20             25             30
Pro Asp Lys Asp Gly Lys Ala Asp Pro Leu Gly Leu Glu Ala Glu Lys
  35             40             45
Asp Gly Val Pro Val Phe Lys Tyr Ser Arg Trp Arg Ala Lys Ala Gln
  50             55             60
Ala Leu Pro Asp Val Val Ala Lys Tyr Gln Ala Leu Gly Ala Glu Leu
  65             70             75             80
Asn Val Leu Pro Ser Cys Ser Gln Phe Ile Pro Met Glu Ile Ile Ser
  85             90             95
Ala Pro Arg His Gly Ser Ile Ile Tyr His Pro Ser Leu Leu Pro Arg
  100            105            110
His Arg Gly Ala Ser Ala Ile Asn Trp Thr Leu Ile His Gly Asp Lys
  115            120            125
Lys Gly Gly Phe Ser Ile Phe Trp Ala Asp Asp Gly Leu Asp Thr Gly
  130            135            140
Asp Leu Leu Leu Gln Lys Glu Cys Glu Val Leu Pro Asp Asp Thr Val
  145            150            155            160
Ser Thr Leu Tyr Asn Arg Phe Leu Phe Pro Glu Gly Ile Lys Gly Val
  165            170            175
Val Gln Ala Val Arg Leu Ile Ala Glu Gly Lys Ala Pro Arg Leu Pro
  180            185            190
Gln Pro Lys Glu Gly Ala Thr Tyr Glu Gly Ile Gln Lys Lys Glu Thr
  195            200            205
Ala Lys Ile Asn Trp Asp Gln Pro Ala Glu Ala Ile His Asn Trp Ile
  210            215            220
Arg Gly Asn Asp Lys Val Pro Gly Ala Trp Thr Glu Ala Cys Glu Gln

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225					230					235					240
Lys	Leu	Thr	Phe	Phe	Asn	Ser	Thr	Leu	Asn	Thr	Ser	Gly	Leu	Val	Pro
				245					250					255	
Glu	Gly	Asp	Ala	Leu	Pro	Ile	Pro	Gly	Ala	His	Arg	Pro	Gly	Val	Val
			260					265					270		
Thr	Lys	Ala	Gly	Leu	Ile	Leu	Phe	Gly	Asn	Asp	Asp	Lys	Met	Leu	Leu
		275					280					285			
Val	Lys	Asn	Ile	Gln	Leu	Glu	Asp	Gly	Lys	Met	Ile	Leu	Ala	Ser	Asn
	290					295				300					
Phe	Phe	Lys	Gly	Ala	Ala	Ser	Ser	Val	Leu	Glu	Leu	Thr	Glu	Ala	Glu
305					310					315					320
Leu	Val	Thr	Ala	Glu	Ala	Val	Arg	Ser	Val	Trp	Gln	Arg	Ile	Leu	Pro
			325						330					335	
Lys	Val	Leu	Glu	Val	Glu	Asp	Ser	Thr	Asp	Phe	Phe	Lys	Ser	Gly	Ala
		340						345					350		
Ala	Ser	Val	Asp	Val	Val	Arg	Leu	Val	Glu	Glu	Val	Lys	Glu	Leu	Cys
		355					360					365			
Asp	Gly	Leu	Glu	Leu	Glu	Asn	Glu	Asp	Val	Tyr	Met	Ala	Ser	Thr	Phe
	370					375					380				
Gly	Asp	Phe	Ile	Gln	Leu	Val	Arg	Lys	Leu	Arg	Gly	Asp	Asp	Glu	
385					390				395					400	
Glu	Gly	Glu	Cys	Ser	Ile	Asp	Tyr	Val	Glu	Met	Ala	Val	Asn	Lys	Arg
			405						410					415	
Thr	Val	Arg	Met	Pro	His	Gln	Leu	Phe	Ile	Gly	Gly	Glu	Phe	Val	Asp
		420						425					430		
Ala	Glu	Gly	Ala	Lys	Thr	Ser	Glu	Thr	Ile	Asn	Pro	Thr	Asp	Gly	Ser
		435					440					445			
Val	Ile	Cys	Gln	Val	Ser	Leu	Ala	Gln	Val	Thr	Asp	Val	Asp	Lys	Ala
	450					455				460					
Val	Ala	Ala	Ala	Lys	Gly	Ala	Phe	Glu	Asn	Gly	Arg	Trp	Gly	Lys	Ile
465					470				475						480
Ser	Ala	Arg	Asp	Arg	Gly	Arg	Leu	Met	Tyr	Arg	Leu	Ala	Asp	Leu	Met
			485						490					495	
Glu	Gln	His	Gln	Glu	Glu	Leu	Ala	Thr	Ile	Glu	Ala	Leu	Asp	Ala	Gly
		500						505					510		
Ala	Val	Tyr	Thr	Leu	Ala	Leu	Lys	Thr	His	Val	Gly	Met	Ser	Ile	Gln
		515					520					525			
Thr	Phe	Arg	Tyr	Phe	Ala	Gly	Trp	Cys	Asp	Lys	Ile	Gln	Gly	Ser	Thr
	530					535					540				
Ile	Pro	Ile	Asn	Gln	Ala	Arg	Pro	Asn	Arg	Asn	Leu	Thr	Leu	Thr	Arg
545				550					555						560
Lys	Glu	Pro	Val	Gly	Val	Cys	Gly	Ile	Ile	Ile	Pro	Trp	Asn	Tyr	Pro
			565						570					575	
Leu	Met	Met	Leu	Ser	Trp	Lys	Thr	Ala	Ala	Cys	Leu	Ala	Ala	Gly	Asn
			580					585					590		
Thr	Val	Val	Ile	Lys	Pro	Ala	Gln	Val	Thr	Pro	Leu	Thr	Ala	Leu	Lys
		595					600					605			
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	610					615					620				
Val	Leu	Pro	Gly	Ser	Gly	Ser	Leu	Val	Gly	Gln	Arg	Leu	Ser	Asp	His
625					630					635					640
Pro	Asp	Val	Arg	Lys	Ile	Gly	Phe	Thr	Gly	Ser	Thr	Glu	Val	Gly	Lys
			645						650					655	
His	Ile	Met	Lys	Ser	Cys	Ala	Ile	Ser	Asn	Val	Lys	Lys	Val	Ser	Leu
		660						665					670		
Glu	Leu	Gly	Glu	Ser	Pro	Phe	Ile	Ile	Phe	Ala	Asp	Cys	Asp	Leu	
		675				680					685				
Asn	Lys	Ala	Val	Gln	Met	Gly	Met	Ser	Ser	Val	Phe	Phe	Ser	Lys	Gly
	690					695					700				
Glu	Asn	Cys	Ile	Ala	Ala	Gly	Arg	Leu	Phe	Val	Glu	Asp	Ser	Ile	His
705					710					715					720

Asp Glu Phe Val Arg Arg Val Val Glu Glu Val Arg Lys Met Lys Val
 725 730 735
 Gly Asn Pro Leu Asp Arg Asp Thr Asp His Gly Pro Gln Asn His His
 740 745 750
 Ala His Leu Val Lys Leu Met Glu Tyr Cys Gln His Gly Val Lys Glu
 755 760 765
 Gly Ala Thr Leu Val Cys Gly Gly Asn Gln Val Pro Arg Pro Gly Phe
 770 775 780
 Phe Phe Glu Pro Thr Val Phe Thr Asp Val Glu Asp His Met Phe Ile
 785 790 795 800
 Ala Lys Glu Glu Ser Phe Gly Pro Val Met Ile Ile Ser Arg Phe Ala
 805 810 815
 Asp Gly Asp Leu Asp Ala Val Leu Ser Arg Ala Asn Ala Thr Glu Phe
 820 825 830
 Gly Leu Ala Ser Gly Val Phe Thr Arg Asp Ile Asn Lys Ala Leu Tyr
 835 840 845
 Val Ser Asp Lys Leu Gln Ala Gly Thr Val Phe Val Asn Thr Tyr Asn
 850 855 860
 Lys Thr Asp Val Ala Ala Pro Phe Gly Gly Phe Lys Gln Ser Gly Phe
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<211> 3095

<212> DNA

<213> Homosapien

<400> 97

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Ala	Val	Val	Ala	Arg	Lys	Leu	Glu	Leu	Thr	Lys	Ala	Glu	Lys	His	Val	
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 <213> Homosapien

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 <212> PRT
 <213> Homosapien

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Pro Pro Gly Arg Ala Ser Pro Gly Arg Ala Ser Pro Ala Gln Ala Ser		
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Pro Ala Arg Ala Ser Pro Ala Leu Ala Ser Leu Ser Arg Ser Ser Ser		
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Gly Arg Ser Ser Ser Ala Arg Ser Ala Ser Val Thr Thr Ser Pro Thr		
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Arg Val Tyr Leu Val Arg Ala Thr Pro Val Gly Ala Val Pro Ile Arg		
115	120	125
Ser Ser Pro Ala Arg Ser Ala Pro Ala Thr Arg Ala Thr Arg Glu Ser		
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Pro Gly Thr Ser Leu Pro Lys Phe Thr Trp Arg Glu Gly Gln Lys Gln		
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Leu Ile Ile Leu Phe Gln Phe Trp Gln Gly His Thr Gly Ile Arg His		
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Lys Glu Gln Arg Glu Ser Cys Pro Lys His Ala Val Arg Cys Asp Gly		
195	200	205
Val Val Asp Cys Lys Leu Lys Ser Asp Glu Leu Gly Cys Val Arg Phe		
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Asp Trp Asp Lys Ser Leu Leu Lys Ile Tyr Ser Gly Ser Ser His Gln		
225	230	235
Trp Leu Pro Ile Cys Ser Ser Asn Trp Asn Asp Ser Tyr Ser Glu Lys		
245	250	255
Thr Cys Gln Gln Leu Gly Phe Glu Ser Ala His Arg Thr Thr Glu Val		
260	265	270
Ala His Arg Asp Phe Ala Asn Ser Phe Ser Ile Leu Arg Tyr Asn Ser		
275	280	285
Thr Ile Gln Glu Ser Leu His Arg Ser Glu Cys Pro Ser Gln Arg Tyr		
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Ser Leu His Phe Gly Thr Thr His Ile Cys Gly Gly Thr Leu Ile Asp		
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Ala Gln Trp Val Leu Thr Ala Ala His Cys Phe Phe Val Thr Arg Glu		
355	360	365
Lys Val Leu Glu Gly Trp Lys Val Tyr Ala Gly Thr Ser Asn Leu His		
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Gln Leu Pro Glu Ala Ala Ser Ile Ala Glu Ile Ile Ile Asn Ser Asn		
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 <211> 2263
 <212> DNA
 <213> Homosapien

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<400> 102

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 35 40 45
 Val Val Asp Ile Ala His Ser Pro Pro Ala Lys Lys Lys Ser Thr Gly
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 65 70 75 80
 Lys Ala Ala Ser Gly Ser Thr Gly Asp Gln Lys Val Gln Ile Ser Tyr
 85 90 95
 Tyr Gly Pro Lys Thr Pro Pro Val Lys Ala Leu Leu Tyr Leu Thr Ala
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 Val Glu Ile Ser Leu Cys Ala Asp Ile Thr Arg Thr Gly Lys Val Lys
 115 120 125
 Pro Thr Arg Ala Val Lys Asp Gln Arg Thr Trp Thr Trp Gly Pro Cys
 130 135 140
 Gly Gln Gly Ala Ile Leu Leu Val Asn Cys Asp Arg Asp Asn Leu Glu
 145 150 155 160
 Ser Ser Ala Met Asp Cys Glu Asp Asp Glu Val Leu Asp Ser Glu Asp
 165 170 175
 Leu Gln Asp Met Ser Leu Met Thr Leu Ser Thr Lys Thr Pro Lys Asp
 180 185 190
 Phe Phe Thr Asn His Thr Leu Val Leu His Val Ala Arg Ser Glu Met
 195 200 205
 Asp Lys Val Arg Val Phe Gln Ala Thr Arg Gly Lys Leu Ser Ser Lys
 210 215 220
 Cys Ser Val Val Leu Gly Pro Lys Trp Pro Ser His Tyr Leu Met Val
 225 230 235 240
 Pro Gly Gly Lys His Asn Met Asp Phe Tyr Val Glu Ala Leu Ala Phe
 245 250 255
 Pro Asp Thr Asp Phe Pro Gly Leu Ile Thr Leu Thr Ile Ser Leu Leu
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 Asp Thr Ser Asn Leu Glu Leu Pro Glu Ala Val Val Phe Gln Asp Ser
 275 280 285
 Val Val Phe Arg Val Ala Pro Trp Ile Met Thr Pro Asn Thr Gln Pro
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 Pro Gln Glu Val Tyr Ala Cys Ser Ile Phe Glu Asn Glu Asp Phe Leu
 305 310 315 320
 Lys Ser Val Thr Thr Leu Ala Met Lys Ala Lys Cys Lys Leu Thr Ile
 325 330 335
 Cys Pro Glu Glu Glu Asn Met Asp Asp Gln Trp Met Gln Asp Glu Met
 340 345 350
 Glu Ile Gly Tyr Ile Gln Ala Pro His Lys Thr Leu Pro Val Val Phe
 355 360 365
 Asp Ser Pro Arg Asn Arg Gly Leu Lys Glu Phe Pro Ile Lys Arg Val
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 Met Gly Pro Asp Phe Gly Tyr Val Thr Arg Gly Pro Gln Thr Gly Gly
 385 390 395 400
 Ile Ser Gly Leu Asp Ser Phe Gly Asn Leu Glu Val Ser Pro Pro Val
 405 410 415
 Thr Val Arg Gly Lys Glu Tyr Pro Leu Gly Arg Ile Leu Phe Gly Asp
 420 425 430
 Ser Cys Tyr Pro Ser Asn Asp Ser Arg Gln Met His Gln Ala Leu Gln
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 Asp Phe Leu Ser Ala Gln Gln Val Gln Ala Pro Val Lys Leu Tyr Ser
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 Asp Trp Leu Ser Val Gly His Val Asp Glu Phe Leu Ser Phe Val Pro
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<211> 1204
<212> DNA
<213> Homosapien
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<210> 104
<211> 189
<212> PRT
<213> Homosapien
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 35 40 45
 Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
 50 55 60
 Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
 65 70 75 80
 Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Val His Leu
 85 90 95
 Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
 100 105 110
 Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
 115 120 125
 Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
 130 135 140
 Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
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 Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
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<210> 105

<211> 1637

<212> DNA

<213> Homosapien

<400> 105

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<210> 106

<211> 465

<212> PRT

<213> Homosapien

<400> 106

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Leu Asp Glu Glu Asp Lys Leu Arg His Phe Arg Glu Cys Phe Tyr Ile
        35           40           45
Pro Lys Ile Gln Asp Leu Pro Pro Val Asp Leu Ser Leu Val Asn Lys
       50           55           60
Asp Glu Asn Ala Ile Tyr Phe Leu Gly Asn Ser Leu Gly Leu Gln Pro
      65           70           75           80
Lys Met Val Lys Thr Tyr Leu Glu Glu Glu Leu Asp Lys Trp Ala Lys
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Ile Ala Ala Tyr Gly His Glu Val Gly Lys Arg Pro Trp Ile Thr Gly
        100           105           110
Asp Glu Ser Ile Val Gly Leu Met Lys Asp Ile Val Gly Ala Asn Glu
       115           120           125
Lys Glu Ile Ala Leu Met Asn Ala Leu Thr Val Asn Leu His Leu Leu
      130           135           140
Met Leu Ser Phe Phe Lys Pro Thr Pro Lys Arg Tyr Lys Ile Leu Leu
     145           150           155           160
Glu Ala Lys Ala Phe Pro Ser Asp His Tyr Ala Ile Glu Ser Gln Leu
          165           170           175
Gln Leu His Gly Leu Asn Ile Glu Glu Ser Met Arg Met Ile Lys Pro
        180           185           190
Arg Glu Gly Glu Glu Thr Leu Arg Ile Glu Asp Ile Leu Glu Val Ile
       195           200           205
Glu Lys Glu Gly Asp Ser Ile Ala Val Ile Leu Phe Ser Gly Val His
      210           215           220
Phe Tyr Thr Gly Gln His Phe Asn Ile Pro Ala Ile Thr Lys Ala Gly
     225           230           235           240
Gln Ala Lys Gly Cys Tyr Val Gly Phe Asp Leu Ala His Ala Val Gly
          245           250           255
Asn Val Glu Leu Tyr Leu His Asp Trp Gly Val Asp Phe Ala Cys Trp
        260           265           270
Cys Ser Tyr Lys Tyr Leu Asn Ala Gly Ala Gly Gly Ile Ala Gly Ala
       275           280           285
Phe Ile His Glu Lys His Ala His Thr Ile Lys Pro Ala Leu Val Gly
      290           295           300
Trp Phe Gly His Glu Leu Ser Thr Arg Phe Lys Met Asp Asn Lys Leu
     305           310           315           320
Gln Leu Ile Pro Gly Val Cys Gly Phe Arg Ile Ser Asn Pro Pro Ile
          325           330           335
Leu Leu Val Cys Ser Leu His Ala Ser Leu Glu Ile Phe Lys Gln Ala
        340           345           350
Thr Met Lys Ala Leu Arg Lys Lys Ser Val Leu Leu Thr Gly Tyr Leu
       355           360           365
Glu Tyr Leu Ile Lys His Asn Tyr Gly Lys Asp Lys Ala Ala Thr Lys
      370           375           380
Lys Pro Val Val Asn Ile Ile Thr Pro Ser His Val Glu Glu Arg Gly
     385           390           395           400
Cys Gln Leu Thr Ile Thr Phe Ser Val Pro Asn Lys Asp Val Phe Gln
          405           410           415
Glu Leu Glu Lys Arg Gly Val Val Cys Asp Lys Arg Asn Pro Asn Gly
        420           425           430
Ile Arg Val Ala Pro Val Pro Leu Tyr Asn Ser Phe His Asp Val Tyr
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Lys Phe Thr Asn Leu Leu Thr Ser Ile Leu Asp Ser Ala Glu Thr Lys

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450

455

460

Asn

465

<210> 107

<211> 1647

<212> DNA

<213> Homosapien

<400> 107

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<210> 108

<211> 383

<212> PRT

<213> Homosapien

<400> 108

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          20           25           30
Pro Ala Tyr Arg Leu Pro Val Val Leu Pro Gln Ser Thr Leu Asn Leu
          35           40           45
Ala Lys Pro Asp Phe Gly Ala Glu Ala Lys Leu Glu Val Ser Ser Ser
          50           55           60
Cys Gly Pro Gln Cys His Lys Gly Thr Pro Leu Pro Thr Tyr Glu Glu
65           70           75           80
Ala Lys Gln Tyr Leu Ser Tyr Glu Thr Leu Tyr Ala Asn Gly Ser Arg
          85           90           95
Thr Glu Thr Gln Val Gly Ile Tyr Ile Leu Ser Ser Ser Gly Asp Gly
          100          105          110
Ala Gln His Arg Asp Ser Gly Ser Ser Gly Lys Ser Arg Arg Lys Arg

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Ser	Thr	Ser	Ala	Met	Pro	Glu	Gln	Met	Lys	Phe	Gln	Trp	Ile	Arg	Val
210						215					220				
Lys	Arg	Thr	His	Val	Pro	Lys	Gly	Trp	Ile	Lys	Gly	Asn	Ala	Asn	Asp
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Pro	Gly	Gly	Arg	Ile	His	Phe	Ser	Gly	Tyr	Asp	Asn	Asp	Arg	Pro	Gly
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Asn	Leu	Val	Tyr	Arg	Phe	Cys	Asp	Val	Lys	Asp	Glu	Thr	Tyr	Asp	Leu
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Leu	Tyr	Gln	Gln	Cys	Asp	Ala	Gln	Pro	Gly	Ala	Ser	Gly	Ser	Gly	Val
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Tyr	Val	Arg	Met	Trp	Lys	Arg	Gln	Gln	Gln	Lys	Trp	Glu	Arg	Lys	Ile
			325						330					335	
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Gln	Asp	Phe	Asn	Val	Ala	Val	Arg	Ile	Thr	Pro	Leu	Lys	Tyr	Ala	Gln
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<210> 109

<211> 5375

<212> DNA

<213> Homosapien

<400> 109

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<210> 110
 <211> 1531
 <212> PRT
 <213> Homosapien

<400> 110

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Cys Ser Gln Met Pro Ala Phe Ser Glu Pro Ala Gly Glu Glu Ser Pro
           35           40           45
Phe Thr Gly Thr Thr Thr Ile Ser Phe Ser Asn Leu Gly Gly Val His
           50           55           60
Lys Glu Asn Ala Ser Leu Ala Gln His Ser Glu Val Lys Pro Cys Thr
           65           70           75           80
Cys Gly Pro Gln Gln Glu Glu Lys Gln Asp Arg Asp Gly Asn Ile Pro
           85           90           95
Asp Asn Phe Arg Glu Asp Leu Lys Tyr Glu Gln Ser Ile Ser Glu Ala
           100          105          110
Asn Asp Glu Thr Met Ser Pro Gly Val Phe Ser Arg His Leu Pro Lys
           115          120          125
Asp Ala Arg Ala Asp Phe Arg Glu Pro Val Ala Val Ser Val Ala Ser
           130          135          140
Pro Glu Pro Thr Asp Thr Ala Leu Thr Leu Glu Asn Val Cys Asp Glu
           145          150          155          160
Pro Arg Asp Arg Glu Ala Val Cys Ala Met Glu Cys Phe Glu Ala Ser
           165          170          175
Asp Gln Gly Thr Cys Phe Asp Thr Ile Asp Ser Leu Val Gly Thr Pro
           180          185          190
Val Asp Asn Tyr Ser Pro Gln Glu Ile Cys Ser Val Asp Thr Glu Leu
           195          200          205
Ala Glu Gly Gln Asn Lys Val Ser Asp Leu Cys Ser Ser Asn Asp Lys
           210          215          220
Thr Leu Glu Val Phe Phe Gln Thr Gln Val Ser Glu Thr Ser Val Ser
           225          230          235          240
Thr Cys Lys Ser Ser Lys Asp Gly Asn Ser Val Met Ser Pro Leu Phe
           245          250          255
Ile Ser Thr Phe Thr Leu Asn Ile Ser His Thr Ala Ser Glu Gly Ala
           260          265          270
Thr Gly Glu Asn Leu Ala Lys Val Glu Lys Ser Thr Tyr Pro Leu Ala
           275          280          285
Ser Thr Val His Ala Gly Gln Glu Gln Pro Ser Pro Ser Asn Ser Gly
           290          295          300
Gly Leu Asp Glu Thr Gln Leu Leu Ser Ser Glu Asn Asn Pro Leu Val
           305          310          315          320
Gln Phe Lys Glu Gly Gly Asp Lys Ser Pro Ser Pro Ser Ala Ala Asp
           325          330          335
Thr Thr Ala Thr Pro Ala Ser Tyr Ser Ser Ile Val Ser Phe Pro Trp

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Glu Gly Ser Met Lys Gln Glu Ala Glu Gln Ile Gln Pro Glu Glu Ala
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 Lys Thr Ala Ile Trp Gln Val Leu Gln Pro Ser Glu Gly Gly Glu Arg
 850 855 860
 Ile Pro Ser Gly Cys Ser Ile Gly Gln Ile Gln Glu Ser Ser Asp Gly
 865 870 875 880
 Ser Leu Gly Glu Ala Glu Gln Ser Lys Lys Asp Lys Ala Glu Leu Ile
 885 890 895
 Ser Pro Thr Ser Pro Leu Ser Ser Cys Leu Pro Ile Met Thr His Ser
 900 905 910
 Ser Leu Gly Val Asp Thr His Asn Ser Thr Gly Gln Ile His Asp Val
 915 920 925
 Pro Glu Asn Asp Ile Val Glu Pro Arg Lys Arg Gln Tyr Val Phe Pro
 930 935 940
 Val Ser Gln Lys Arg Gly Thr Ile Glu Asn Glu Arg Gly Lys Pro Leu
 945 950 955 960
 Pro Ser Ser Pro Asp Leu Thr Arg Phe Pro Cys Thr Ser Ser Pro Glu
 965 970 975
 Gly Asn Val Thr Asp Phe Leu Ile Ser His Lys Met Glu Glu Pro Lys
 980 985 990
 Ile Glu Val Leu Gln Ile Gly Glu Thr Lys Pro Pro Ser Ser Ser
 995 1000 1005
 Ser Ser Ala Lys Thr Leu Ala Phe Ile Ser Gly Glu Arg Glu Leu Glu
 1010 1015 1020
 Lys Ala Pro Lys Leu Leu Gln Asp Pro Cys Gln Lys Gly Thr Leu Gly
 1025 1030 1035 1040
 Cys Ala Lys Lys Ser Arg Glu Arg Glu Lys Ser Leu Glu Ala Arg Ala
 1045 1050 1055
 Gly Lys Ser Pro Gly Thr Leu Thr Ala Val Thr Gly Ser Glu Glu Val
 1060 1065 1070
 Lys Arg Lys Pro Glu Ala Pro Gly Ser Gly His Leu Ala Glu Gly Val
 1075 1080 1085

 Lys Lys Lys Ile Leu Ser Arg Val Ala Ala Leu Arg Leu Lys Leu Glu
 1090 1095 1100
 Glu Lys Glu Asn Ile Arg Lys Asn Ser Ala Phe Leu Lys Lys Met Pro
 1105 1110 1115 1120
 Lys Leu Glu Thr Ser Leu Ser His Thr Glu Glu Lys Gln Asp Pro Lys
 1125 1130 1135
 Lys Pro Ser Cys Lys Arg Glu Gly Arg Ala Pro Val Leu Leu Lys Lys
 1140 1145 1150
 Ile Gln Ala Glu Met Phe Pro Glu His Ser Gly Asn Val Lys Leu Ser
 1155 1160 1165
 Cys Gln Phe Ala Glu Ile His Glu Asp Ser Thr Ile Cys Trp Thr Lys
 1170 1175 1180
 Asp Ser Lys Ser Ile Ala Gln Val Gln Arg Ser Ala Gly Asp Asn Ser
 1185 1190 1195 1200
 Thr Val Ser Phe Ala Ile Val Gln Ala Ser Pro Lys Asp Gln Gly Leu
 1205 1210 1215
 Tyr Tyr Cys Cys Ile Lys Asn Ser Tyr Gly Lys Val Thr Ala Glu Phe
 1220 1225 1230
 Asn Leu Thr Ala Glu Val Leu Lys Gln Leu Ser Ser Arg Gln Asp Thr
 1235 1240 1245
 Lys Gly Cys Glu Glu Ile Glu Phe Ser Gln Leu Ile Phe Lys Glu Asp
 1250 1255 1260
 Phe Leu His Asp Ser Tyr Phe Gly Gly Arg Leu Arg Gly Gln Ile Ala
 1265 1270 1275 1280
 Thr Glu Glu Leu His Phe Gly Glu Gly Val His Arg Lys Ala Phe Arg
 1285 1290 1295
 Ser Thr Val Met His Gly Leu Met Pro Val Phe Lys Pro Gly His Ala
 1300 1305 1310

Cys Val Leu Lys Val His Asn Ala Ile Ala Tyr Gly Thr Arg Asn Asn
 1315 1320 1325
 Asp Glu Leu Ile Gln Arg Asn Tyr Lys Leu Ala Ala Gln Glu Cys Tyr
 1330 1335 1340
 Val Gln Asn Thr Ala Arg Tyr Tyr Ala Lys Ile Tyr Ala Ala Glu Ala
 1345 1350 1355 1360
 Gln Pro Leu Glu Gly Phe Gly Glu Val Pro Glu Ile Ile Pro Ile Phe
 1365 1370 1375
 Leu Ile His Arg Pro Glu Asn Asn Ile Pro Tyr Ala Thr Val Glu Glu
 1380 1385 1390
 Glu Leu Ile Gly Glu Phe Val Lys Tyr Ser Ile Arg Asp Gly Lys Glu
 1395 1400 1405
 Ile Asn Phe Leu Arg Arg Glu Ser Glu Ala Gly Gln Lys Cys Cys Thr
 1410 1415 1420
 Phe Gln His Trp Val Tyr Gln Lys Thr Ser Gly Cys Leu Leu Val Thr
 1425 1430 1435 1440
 Asp Met Gln Gly Val Gly Met Lys Leu Thr Asp Val Gly Ile Ala Thr
 1445 1450 1455
 Leu Ala Lys Gly Tyr Lys Gly Phe Lys Gly Asn Cys Ser Met Thr Phe
 1460 1465 1470
 Ile Asp Gln Phe Lys Ala Leu His Gln Cys Asn Lys Tyr Cys Lys Met
 1475 1480 1485
 Leu Gly Leu Lys Ser Leu Gln Asn Asn Asn Gln Lys Gln Lys Gln Pro
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 Ala Gly Pro Glu Thr Pro Gly Glu Lys Lys Thr
 1525 1530

<210> 111
 <211> 1241
 <212> DNA
 <213> Homosapien

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 gcctgctggg ccctgctgcc gcccgtgccc tgctgcttgg gctgcctggc cgaacgctgg 240
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 ccgaatatgt tgtcaatgac gagaattggc ttggccccag ttctgggcta tttgattatt 480
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<210> 112

<211> 301
 <212> PRT
 <213> Homosapien

<400> 112

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 20           25           30
Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu Arg
 35           40           45
Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile Gly
 50           55           60
Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro Ala
 65           70           75           80
Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly Pro
 85           90           95
Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn Met
 100          105          110
Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu Ile
 115          120          125
Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala Gly
 130          135          140
Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn Gln
 145          150          155          160
Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile Leu
 165          170          175
Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro Val
 180          185          190
Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala Ala
 195          200          205
Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu Ala
 210          215          220
Lys Tyr Phe Asn Pro Cys Tyr Ala Thr Ala Arg Leu Lys Pro Thr Phe
 225          230          235          240
Ile Ser Lys Val Asn Thr Ala Val Gln Leu Ile Leu Val Ala Ala Ser
 245          250          255
Leu Ala Ala Pro Val Phe Asn Tyr Ala Asp Ser Ile Tyr Leu Gln Ile
 260          265          270
Leu Trp Cys Phe Thr Ala Phe Thr Thr Ala Ala Ser Ala Tyr Ser Tyr
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Tyr His Tyr Gly Arg Lys Thr Val Gln Val Ile Lys Asp
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<210> 113
 <211> 2906
 <212> DNA
 <213> Homosapien

<400> 113

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aggtctttca ttgggactcc ctactggatg gctcccgagg tggctgctgt ggagcgcaaa 600

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<210> 114

<211> 765

<212> PRT

<213> Homosapien

<220>

<221> VARIANT

<222> (1)...(765)

<223> Xaa = Any Amino Acid

<400> 114

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      20           25           30
Ala Gly Asn His His Pro Ala Val Pro Pro Pro Gln Cys Gly Gly Leu

      35           40           45
His Trp Gln Leu Pro Gln Glu Pro Leu Val Asp Leu His Gly Val Leu
      50           55           60
Arg Arg Gly Leu Pro Ala Gly Asp Leu Pro Cys His Trp Ala Pro Gly

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Gly	Ala	Ala	Asp	Cys	Leu	Arg	Leu	Pro	Arg	Ala	Thr	Glu	Gly	Ala	Pro
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Pro	Pro	Ala	Phe	Ser	Gly	Glu	Asp	Pro	Gln	Arg	His	Gln	Gly	Ser	Gln
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Pro	Ser	Pro	His	Ser	Pro	Gly	Arg	Cys	Gln	Thr	Gly	Leu	Trp	Gly	Val
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Arg	Arg	Ala	Asp	Ser	Val	Cys	Gly	Gln	Glu	Glu	Val	Phe	His	Trp	Asp
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Ser	Leu	Leu	Asp	Gly	Ser	Arg	Gly	Gly	Cys	Cys	Gly	Ala	Gln	Arg	Trp
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Leu	Gln	Ala	Met	Arg	Leu	Gly	Pro	Gly	His	His	Cys	His	Ala	Gly	Arg
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Ala	Ala	Ala	Pro	Ser	Val	Pro	Pro	Ala	Pro	His	Glu	Gly	Pro	Asp	Ala
		180						185					190		
His	Val	Glu	Glu	Gln	Leu	Pro	Ala	Ala	Gln	Thr	Glu	Arg	Asp	Ser	Leu
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Asp	Pro	Glu	Phe	Pro	Pro	Leu	Ser	Gln	Thr	Gly	Pro	Asp	Gln	Glu	Ser
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Glu	Glu	Ala	Asp	Ser	Arg	Glu	Ala	Pro	Ala	Ala	Pro	Val	His	Asp	Ser
225					230				235					240	
Ala	Ala	Pro	Ser	Gly	Pro	Pro	His	Thr	Ala	Ala	Gly	Gln	Ser	Gln	Pro
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Ser	Ser	Gly	Asp	Pro	Leu	Pro	Gly	Leu	Ala	Gly	Asp	Leu	His	Val	Ser
		260				265						270			
Arg	His	His	Ser	Leu	Pro	Gly	Ala	Ala	Arg	Pro	Ser	Arg	Glu	Asp	Pro
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Leu	Gly	Asp	Pro	Val	Ser	Pro	Gly	Glu	Ile	Trp	Arg	Pro	Thr	Gln	Glu
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Gly	Asn	Pro	Thr	Glu	Ala	Val	Gly	Gly	Arg	Val	Asp	Thr	Thr	Gly	Lys
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Gly	Arg	Val	Glu	Trp	Glu	Pro	Ala	Ala	Val	Gly	Pro	Gly	Gly	Pro	Gly
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Gly	Lys	Glu	Ser	Asp	Tyr	Ser	Val	Ser	Leu	Arg	Ile	Pro	Gly	Ala	Gly
		340						345					350		
Leu	Pro	Arg	Arg	Tyr	His	Gly	Asn	His	Gln	Ala	Gly	Pro	Val	Pro	Arg
		355				360						365			
Ala	Thr	Pro	His	Pro	Ser	Ser	Arg	Gly	Ala	Ser	Val	Gln	Ser	Pro	Arg
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Asn	Pro	Ala	Pro	Thr	Ser	Phe	Arg	Pro	Gln	Gln	Leu	Pro	Thr	Ala	Ala
385					390				395					400	
His	Gly	Leu	Gly	His	His	Glu	Ala	Ala	Gly	Gly	Ser	Glu	Val	Ile	Leu
			405						410					415	
Pro	Arg	Ala	Pro	Pro	Asn	Ser	Gln	Gly	Ala	Tyr	Gly	Arg	Leu	Leu	Leu
		420						425				430			
Gln	Gly	Leu	Gln	Trp	Leu	Pro	Pro	Ala	Asp	Pro	Arg	Cys	Cys	His	Leu
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Asp	Ser	Pro	Cys	Tyr	Ser	Gly	Pro	Val	Pro	Gly	Gly	Arg	Gly	Arg	Gly
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Arg	His	Leu	His	Thr	Gln	Pro	Ala	Thr	Ala	Gly	Tyr	Ala	Gly	Glu	Ala
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Val	Thr	Leu	Arg	Glu	Ile	His	Ala	His	Leu	Gly	Pro	Pro	Pro	Arg	Pro
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		530				535					540				
Asp	Ser	His	Gln	Arg	Leu	Leu	Ala	Val	Ser	Cys	Gly	Ala	Glu	Pro	Leu
545					550					555				560	

His Gly Cys His Leu Pro Ala Gly Arg Pro Ala His Gln Pro Ala Pro
 565 570 575
 Ala Ala Val Val Ala Ala Ala Glu Val Ser Ala Ala Glu Glu Leu Leu
 580 585 590
 Gln Pro Ser Ala Gln Pro Ser Trp Asp Ala Gly Ala Ala Gly Ala Gly
 595 600 605
 Trp Glu Gly Ala Ala Ala Gly Val Cys Trp Gly Arg Gly Ala Gly Ala
 610 615 620
 Arg Leu Pro Arg Pro Val Pro Cys Pro Ala Pro Gly Gly Trp Pro Asp
 625 630 635 640
 Ala Arg His Pro His Pro Thr Gly Asp Pro Arg Leu Gly Pro Ala Gly
 645 650 655
 Asp Pro Gly Gly Gln Gly His Asn Pro Ser Gln Leu Thr Leu Cys Glu
 660 665 670
 Asp Cys Gln His Ala Gly Arg Ala His Gly His Thr Gly Thr Ala Asp
 675 680 685
 Leu Phe Pro His Arg Asp Cys Gly Val Pro Ala Gly Gln Cys Ala Gly
 690 695 700
 Leu Leu Glu Pro Trp Asp Ala Arg Pro Lys Pro Gly Tyr Gln Gly Asp
 705 710 715 720
 Pro Gly Asp His Arg Asn Lys Asp Leu Pro Ser Ala Trp Gly Pro Gln
 725 730 735
 Arg His His Pro Gly Glu His Ser His Gln Pro Arg Gly Ala Gln Gln
 740 745 750
 Pro Leu His Pro His Gly Pro Pro Glu His Leu Leu Xaa
 755 760 765

<210> 115

<211> 3335

<212> DNA

<213> Homosapien

<220>

<221> misc_feature

<222> (1)...(3335)

<223> n = A,T,C or G

<400> 115

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<210> 116

<211> 416

<212> PRT

<213> Homosapien

<400> 116

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Met Ala His Ser Pro Val Ala Val Gln Val Pro Gly Met Gln Asn Asn
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Ile Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Arg Ile Gly Lys
      20             25             30
Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg Thr Gln Gln
      35             40             45
Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile
      50             55             60
Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Ser
      65             70             75             80
Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Gly Ser Lys Leu Trp
      85             90             95
Ile Ile Met Glu Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Arg
      100            105            110
Ala Gly Pro Phe Asp Glu Phe Gln Ile Ala Thr Met Leu Lys Glu Ile
      115            120            125
Leu Lys Gly Leu Asp Tyr Leu His Ser Glu Lys Lys Ile His Arg Asp
      130            135            140
Ile Lys Ala Ala Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys Leu

```

145		150		155		160
Ala Asp Phe Gly Val	Ala Gly Gln Leu Thr	Asp Thr Gln Ile Lys Arg				
	165	170			175	
Asn Thr Phe Val Gly Thr	Pro Phe Trp Met	Ala Pro Glu Val Ile Gln				
	180	185			190	
Gln Ser Ala Tyr Asp Ser	Lys Ala Asp Ile Trp	Ser Leu Gly Ile Thr				
	195	200			205	
Ala Ile Glu Leu Ala Lys	Gly Glu Pro Pro	Asn Ser Asp Met His Pro				
	210	215			220	
Met Arg Val Leu Phe Leu	Ile Pro Lys Asn	Asn Pro Pro Thr Leu Val				
	225	230			235	240
Gly Asp Phe Thr Lys Ser	Phe Lys Glu Phe	Ile Asp Ala Cys Leu Asn				
	245	250			255	
Lys Asp Pro Ser Phe Arg	Pro Thr Ala Lys	Glu Leu Leu Lys His Lys				
	260	265			270	
Phe Ile Val Lys Asn Ser	Lys Lys Thr Ser Tyr	Leu Thr Glu Leu Ile				
	275	280			285	
Asp Arg Phe Lys Arg Trp	Lys Ala Glu Gly His	Ser Asp Asp Glu Ser				
	290	295			300	
Asp Ser Glu Gly Ser Asp	Ser Glu Ser Thr Ser	Arg Glu Asn Asn Thr				
	305	310			315	320
His Pro Glu Trp Ser Phe	Thr Thr Val Arg	Lys Lys Pro Asp Pro Lys				
	325	330			335	
Lys Val Gln Asn Gly Ala	Glu Gln Asp Leu Val	Gln Thr Leu Ser Cys				
	340	345			350	
Leu Ser Met Ile Ile Thr	Pro Ala Phe Ala	Glu Leu Lys Gln Gln Asp				
	355	360			365	
Glu Asn Asn Ala Ser Arg	Asn Gln Ala Ile Glu	Glu Leu Glu Lys Ser				
	370	375			380	
Ile Ala Val Ala Glu Ala	Ala Cys Pro Gly Ile	Thr Asp Lys Met Val				
	385	390			395	400
Lys Lys Leu Ile Glu Lys	Phe Gln Lys Cys Ser	Ala Asp Glu Ser Pro				
	405	410			415	

<210> 117

<211> 1800

<212> DNA

<213> Homosapien

<400> 117

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tgagcgagct ggcgctgggc cgctggctgc aggagagccg ccgctcgcgg aagctcatcc 180
tgttcatcgt gttcctggcg ctgctgctgg acaacatgct gctcactgtc gtgggtcccca 240
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cacagcacat ggtgaccaac gcgtccgctg ttctttccga ctgtcccagt gaagacaaag 480
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aaagtgttta attgtataaa acagtgtttc cagtgcacac actcatccag aactgtctta 1740
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<210> 118

<211> 514

<212> PRT

<213> Homosapien

<400> 118

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Met Ala Leu Ser Glu Leu Ala Leu Val Arg Trp Leu Gln Glu Ser Arg
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Arg Ser Arg Lys Leu Ile Leu Phe Ile Val Phe Leu Ala Leu Leu Leu
      20          25          30
Asp Asn Met Leu Leu Thr Val Val Val Pro Ile Ile Pro Ser Tyr Leu
      35          40          45
Tyr Ser Ile Lys His Glu Lys Asn Ala Thr Glu Ile Gln Thr Ala Arg
      50          55          60
Pro Val His Thr Ala Ser Ile Ser Asp Ser Phe Gln Ser Ile Phe Ser
      65          70          75          80
Tyr Tyr Asp Asn Ser Thr Met Val Thr Gly Asn Ala Thr Arg Asp Leu
      85          90          95
Thr Leu His Gln Thr Ala Thr Gln His Met Val Thr Asn Ala Ser Ala
      100          105          110
Val Pro Ser Asp Cys Pro Ser Glu Asp Lys Asp Leu Leu Asn Glu Asn
      115          120          125

Val Gln Val Gly Leu Leu Phe Ala Ser Lys Ala Thr Val Gln Leu Ile
      130          135          140
Thr Asn Pro Phe Ile Gly Leu Leu Thr Asn Arg Ile Gly Tyr Pro Ile
      145          150          155          160
Pro Ile Phe Ala Gly Phe Cys Ile Met Phe Val Ser Thr Ile Met Phe
      165          170          175
Ala Phe Ser Ser Ser Tyr Ala Phe Leu Leu Ile Ala Arg Ser Leu Gln
      180          185          190
Gly Ile Gly Ser Ser Cys Ser Ser Val Ala Gly Met Gly Met Leu Ala
      195          200          205
Ser Val Tyr Thr Asp Asp Glu Glu Arg Gly Asn Val Met Gly Ile Ala
      210          215          220
Leu Gly Gly Leu Ala Met Gly Val Leu Val Gly Pro Pro Phe Gly Ser
      225          230          235          240
Val Leu Tyr Glu Phe Val Gly Lys Thr Ala Pro Phe Leu Val Leu Ala
      245          250          255
Ala Leu Val Leu Leu Asp Gly Ala Ile Gln Leu Phe Val Leu Gln Pro
      260          265          270
Ser Arg Val Gln Pro Glu Ser Gln Lys Gly Thr Pro Leu Thr Thr Leu
      275          280          285
Leu Lys Asp Pro Tyr Ile Leu Ile Ala Ala Gly Ser Ile Cys Phe Ala
      290          295          300
Asn Met Gly Ile Ala Met Leu Glu Pro Ala Leu Pro Ile Trp Met Met
      305          310          315          320
Glu Thr Met Cys Ser Arg Lys Trp Gln Leu Gly Val Ala Phe Leu Pro

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	325		330		335
Ala Ser Ile	Ser Tyr Leu Ile Gly Thr Asn Ile Phe Gly Ile Leu Ala				
	340		345		350
His Lys Met	Gly Arg Trp Leu Cys Ala Leu Leu Gly Met Ile Ile Val				
	355		360		365
Gly Val Ser	Ile Leu Cys Ile Pro Phe Ala Lys Asn Ile Tyr Gly Leu				
	370		375		380
Ile Ala Pro	Asn Phe Gly Val Gly Phe Ala Ile Gly Met Val Asp Ser				
385		390		395	400
Ser Met Met	Pro Ile Met Gly Tyr Leu Val Asp Leu Arg His Val Ser				
	405		410		415
Val Tyr Gly	Ser Val Tyr Ala Ile Ala Asp Val Ala Phe Cys Met Gly				
	420		425		430
Tyr Ala Ile	Gly Pro Ser Ala Gly Gly Ala Ile Ala Lys Ala Ile Gly				
	435		440		445
Phe Pro Trp	Leu Met Thr Ile Ile Gly Ile Ile Asp Ile Leu Phe Ala				
	450		455		460
Pro Leu Cys	Phe Phe Leu Arg Ser Pro Pro Ala Lys Glu Glu Lys Met				
465		470		475	480
Ala Ile Leu	Met Asp His Asn Cys Pro Ile Lys Thr Lys Met Tyr Thr				
	485		490		495
Gln Asn Asn	Ile Gln Ser Tyr Pro Ile Gly Glu Asp Glu Glu Ser Glu				
	500		505		510
Ser Asp					

<210> 119
 <211> 2157
 <212> DNA
 <213> Homosapien

<400> 119

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cgtcatattc	cagctctgaa	cagcaacatg	gggtgcaaag	tcctgctcaa	cattgggcag	180
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<210> 120

<211> 629

<212> PRT

<213> Homosapien

<400> 120

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20          25          30
Asn Thr Phe Asp Leu Val Ala Leu Gly Val Gly Ser Thr Leu Gly Ala
35          40          45
Gly Val Tyr Val Leu Ala Gly Ala Val Ala Arg Glu Asn Ala Gly Pro
50          55          60
Ala Ile Val Ile Ser Phe Leu Ile Ala Ala Leu Ala Ser Val Leu Ala
65          70          75          80
Gly Leu Cys Tyr Gly Glu Phe Gly Ala Arg Val Pro Lys Thr Gly Ser
85          90          95
Ala Tyr Leu Tyr Ser Tyr Val Thr Val Gly Glu Leu Trp Ala Phe Ile
100         105         110
Thr Gly Trp Asn Leu Ile Leu Ser Tyr Ile Ile Gly Thr Ser Ser Val
115         120         125
Ala Arg Ala Trp Ser Ala Thr Phe Asp Glu Leu Ile Gly Arg Pro Ile
130         135         140
Gly Glu Phe Ser Arg Thr His Met Thr Leu Asn Ala Pro Gly Val Leu
145         150         155         160
Ala Glu Asn Pro Asp Ile Phe Ala Val Ile Ile Ile Leu Ile Leu Thr
165         170         175
Gly Leu Leu Thr Leu Gly Val Lys Glu Ser Ala Met Val Asn Lys Ile
180         185         190
Phe Thr Cys Ile Asn Val Leu Val Leu Gly Phe Ile Met Val Ser Gly
195         200         205
Phe Val Lys Gly Ser Val Lys Asn Trp Gln Leu Thr Glu Glu Asp Phe
210         215         220
Gly Asn Thr Ser Gly Arg Leu Cys Leu Asn Asn Asp Thr Lys Glu Gly
225         230         235         240
Lys Pro Gly Val Gly Gly Phe Met Pro Phe Gly Phe Ser Gly Val Leu
245         250         255
Ser Gly Ala Ala Thr Cys Phe Tyr Ala Phe Val Gly Phe Asp Cys Ile
260         265         270
Ala Thr Thr Gly Glu Glu Val Lys Asn Pro Gln Lys Ala Ile Pro Val
275         280         285
Gly Ile Val Ala Ser Leu Leu Ile Cys Phe Ile Ala Tyr Phe Gly Val
290         295         300
Ser Ala Ala Leu Thr Leu Met Met Pro Tyr Phe Cys Leu Asp Asn Asn
305         310         315         320
Ser Pro Leu Pro Asp Ala Phe Lys His Val Gly Trp Glu Gly Ala Lys
325         330         335
Tyr Ala Val Ala Val Gly Ser Leu Cys Ala Leu Ser Ala Ser Leu Leu
340         345         350
Gly Ser Met Phe Pro Met Pro Arg Val Ile Tyr Ala Met Ala Glu Asp

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355	360	365
Gly Leu Leu Phe Lys Phe Leu Ala Asn Val Asn Asp Arg Thr Lys Thr		
370	375	380
Pro Ile Ile Ala Thr Leu Ala Ser Gly Ala Val Ala Ala Val Met Ala		
385	390	395
Phe Leu Phe Asp Leu Lys Asp Leu Val Asp Leu Met Ser Ile Gly Thr		
405	410	415
Leu Leu Ala Tyr Ser Leu Val Ala Ala Cys Val Leu Val Leu Arg Tyr		
420	425	430
Gln Pro Glu Gln Pro Asn Leu Val Tyr Gln Met Ala Ser Thr Ser Asp		
435	440	445
Glu Leu Asp Pro Ala Asp Gln Asn Glu Leu Ala Ser Thr Asn Asp Ser		
450	455	460
Gln Leu Gly Phe Leu Pro Glu Ala Glu Met Phe Ser Leu Lys Thr Ile		
465	470	475
Leu Ser Pro Lys Asn Met Glu Pro Ser Lys Ile Ser Gly Leu Ile Val		
485	490	495
Asn Ile Ser Thr Ser Leu Ile Ala Val Leu Ile Ile Thr Phe Cys Ile		
500	505	510
Val Thr Val Leu Gly Arg Glu Ala Leu Thr Lys Gly Ala Leu Trp Ala		
515	520	525
Val Phe Leu Leu Ala Gly Ser Ala Leu Leu Cys Ala Val Val Thr Gly		
530	535	540
Val Ile Trp Arg Gln Pro Glu Ser Lys Thr Lys Leu Ser Phe Lys Val		
545	550	555
Pro Phe Leu Pro Val Leu Pro Ile Leu Ser Ile Phe Val Asn Val Tyr		
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Leu Met Met Gln Leu Asp Gln Gly Thr Trp Val Arg Phe Ala Val Trp		
580	585	590
Met Leu Ile Gly Phe Ile Ile Tyr Phe Gly Tyr Gly Leu Trp His Ser		
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<210> 121

<211> 3807

<212> DNA

<213> Homosapien

<400> 121

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<210> 122

<211> 1268

<212> PRT

<213> Homosapien

<400> 122

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Asn Gly Thr Tyr Gly Gln Val Tyr Lys Gly Arg His Val Lys Thr Gly
      35             40             45
Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Gly Asp Glu Glu Glu
      50             55             60

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Met	Asp	Asp	Gln	Leu	Trp	Leu	Val	Met	Glu	Phe	Cys	Gly	Ala	Gly	Ser
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His	Gln	His	Lys	Val	Ile	His	Arg	Asp	Ile	Lys	Gly	Gln	Asn	Val	Leu
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Gln	Leu	Asp	Arg	Thr	Val	Gly	Arg	Arg	Asn	Thr	Phe	Ile	Gly	Thr	Pro
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Thr	Tyr	Asp	Phe	Lys	Ser	Asp	Leu	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Ile
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Glu	Met	Ala	Glu	Gly	Ala	Pro	Pro	Leu	Cys	Asp	Met	His	Pro	Met	Arg
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Ala	Leu	Phe	Leu	Ile	Pro	Arg	Asn	Pro	Ala	Pro	Arg	Leu	Lys	Ser	Lys
				245					250					255	
Lys	Trp	Ser	Lys	Lys	Phe	Gln	Ser	Phe	Ile	Glu	Ser	Cys	Leu	Val	Lys
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Ile	Arg	Asp	Gln	Pro	Asn	Glu	Arg	Gln	Val	Arg	Ile	Gln	Leu	Lys	Asp
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His	Ile	Asp	Arg	Thr	Lys	Lys	Lys	Arg	Gly	Glu	Lys	Asp	Glu	Thr	Glu
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Tyr	Glu	Tyr	Ser	Gly	Ser	Glu	Glu	Glu	Glu	Glu	Glu	Asn	Asp	Ser	Gly
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Glu	Pro	Ser	Ser	Ile	Leu	Asn	Leu	Pro	Gly	Glu	Ser	Thr	Leu	Arg	Arg
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Asp	Phe	Leu	Arg	Leu	Gln	Leu	Ala	Asn	Lys	Glu	Arg	Ser	Glu	Ala	Leu
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Arg	Arg	Gln	Gln	Leu	Glu	Gln	Gln	Gln	Arg	Glu	Asn	Glu	Glu	His	Lys
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Gln	Arg	Arg	Arg	Leu	Glu	Glu	Gln	Gln	Arg	Arg	Glu	Lys	Glu	Leu	Arg
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Lys	Gln	Gln	Glu	Arg	Glu	Gln	Arg	Arg	His	Tyr	Glu	Glu	Gln	Met	Arg
			420					425					430		
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Lys	Gln	Leu	Glu	Glu	Gln	Arg	Gln	Ala	Glu	Arg	Leu	Gln	Arg	Gln	Leu
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Lys	Gln	Glu	Arg	Asp	Tyr	Leu	Val	Ser	Leu	Gln	His	Gln	Arg	Gln	Glu
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Gln	Arg	Pro	Val	Glu	Lys	Lys	Pro	Leu	Tyr	His	Tyr	Lys	Glu	Gly	Met
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Glu	Asn	Pro	Pro	Leu	Pro	Thr	Arg	Ile	Glu	Lys	Phe	Asp	Arg	Ser	Ser
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Trp	Leu	Arg	Gln	Glu	Glu	Asp	Ile	Pro	Pro	Lys	Val	Pro	Gln	Arg	Thr
			580					585					590		
Thr	Ser	Ile	Ser	Pro	Ala	Leu	Ala	Arg	Lys	Asn	Ser	Pro	Gly	Asn	Gly
		595					600					605			
Ser	Ala	Leu	Gly	Pro	Arg	Leu	Gly	Ser	Gln	Pro	Ile	Arg	Ala	Ser	Asn
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Thr	Ser	Ser	Gly	Ser	Ser	Ser	Ser	Ser	Ser	Thr	Pro	Ser	Ser	Gln	Pro
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Ser	Ser	Gln	Gly	Gly	Ser	Gln	Pro	Gly	Ser	Gln	Ala	Gly	Ser	Ser	Glu
		660						665					670		
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	675						680					685			
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Glu	Leu	Arg	Ile	Glu	Glu	Thr	Asn	Arg	Pro	Met	Lys	Lys	Val	Thr	Asp
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Tyr	Ser	Ser	Ser	Ser	Glu	Glu	Ser	Glu	Ser	Ser	Glu	Glu	Glu	Glu	Glu
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Asp	Gly	Glu	Ser	Glu	Thr	His	Asp	Gly	Thr	Val	Ala	Val	Ser	Asp	Ile
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Pro	Arg	Leu	Ile	Pro	Thr	Gly	Ala	Pro	Gly	Ser	Asn	Glu	Gln	Tyr	Asn
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Val	Gly	Met	Val	Gly	Thr	His	Gly	Leu	Glu	Thr	Ser	His	Ala	Asp	Ser
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Phe	Ser	Gly	Ser	Ile	Ser	Arg	Glu	Gly	Thr	Leu	Met	Ile	Arg	Glu	Thr
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Gly	His	Ile	Asn	Leu	Pro	Asp	Leu	Val	Gln	Gln	Ser	His	Ser	Pro	Ala
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Gly	Thr	Pro	Thr	Glu	Gly	Leu	Gly	Arg	Val	Ser	Thr	His	Ser	Gln	Glu
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Ser	Val	Val	Asn	Val	Asn	Pro	Thr	Asn	Ile	Arg	Pro	His	Ser	Asp	Thr
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Pro	Glu	Ile	Arg	Lys	Tyr	Lys	Lys	Arg	Phe	Asn	Ser	Glu	Ile	Leu	Cys
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Ala	Ala	Leu	Trp	Gly	Val	Asn	Leu	Leu	Val	Gly	Thr	Glu	Asn	Gly	Leu
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Met	Leu	Leu	Asp	Arg	Ser	Gly	Gln	Gly	Lys	Val	Tyr	Asn	Leu	Ile	Asn
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		995						1000					1005		
Val	Thr	Ile	Ser	Gly	Lys	Lys	Asn	Lys	Leu	Arg	Val	Tyr	Tyr	Leu	Ser
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 Gln Gly Trp Ile Thr Val Gly Asp Leu Glu Gly Cys Ile His Tyr Lys
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 Val Val Lys Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala Leu Lys Asn
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 Thr Gly Phe His Val Ile Asp Val Asp Ser Gly Asn Ser Tyr Asp Ile
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 1140 1145 1150
 Ile Leu Pro Lys Thr Asp Gly Met Glu Met Leu Val Cys Tyr Glu Asp
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 Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val Val
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<211> 529

<212> PRT

<213> Homosapien

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          20          25          30
His Tyr Gly Pro Asp Pro Thr Lys Ala Arg Pro Ala Ser Ser Phe Ala
          35          40          45
His Ile Pro Asn Tyr Ser Asn Phe Ser Ser Gln Ala Ile Asn Pro Gly
          50          55          60
Phe Leu Asp Ser Gly Thr Ile Arg Gly Val Ser Gly Ile Gly Val Thr
          65          70          75          80
Leu Phe Ile Ala Leu Tyr Asp Tyr Glu Ala Arg Thr Glu Asp Asp Leu
          85          90          95
Thr Phe Thr Lys Gly Glu Lys Phe His Ile Leu Asn Asn Thr Glu Gly
          100          105          110
Asp Trp Trp Glu Ala Arg Ser Leu Ser Ser Gly Lys Thr Gly Cys Ile
          115          120          125
Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile Gln Ala Glu Glu Trp
          130          135          140
Tyr Phe Gly Lys Ile Gly Arg Lys Asp Ala Glu Arg Gln Leu Leu Ser
          145          150          155          160
Pro Gly Asn Pro Gln Gly Ala Phe Leu Ile Arg Glu Ser Glu Thr Thr
          165          170          175
Lys Gly Ala Tyr Ser Leu Ser Ile Arg Asp Trp Asp Gln Thr Arg Gly
          180          185          190
Asp His Val Lys His Tyr Lys Ile Arg Lys Leu Asp Met Gly Gly Tyr
          195          200          205
Tyr Ile Thr Thr Arg Val Gln Phe Asn Ser Val Gln Glu Leu Val Gln
          210          215          220
His Tyr Met Glu Val Asn Asp Gly Leu Cys Asn Leu Leu Ile Ala Pro
          225          230          235          240
Cys Thr Ile Met Lys Pro Gln Thr Leu Gly Leu Ala Lys Asp Ala Trp
          245          250          255
Glu Ile Ser Arg Ser Ser Ile Thr Leu Glu Arg Arg Leu Gly Thr Gly
          260          265          270
Cys Phe Gly Asp Val Trp Leu Gly Thr Trp Asn Gly Ser Thr Lys Val

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(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
14 August 2003 (14.08.2003)

PCT

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(22) International Filing Date: 29 January 2003 (29.01.2003)

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60/405,450	23 August 2002 (23.08.2002)	US
60/408,070	4 September 2002 (04.09.2002)	US
60/424,300	6 November 2002 (06.11.2002)	US
60/431,042	5 December 2002 (05.12.2002)	US
60/431,079	5 December 2002 (05.12.2002)	US

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(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
18 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOSITIONS FOR TREATING CARDIOVASCULAR DISEASE

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of cardiovascular disease, including, but not limited to, atherosclerosis, reperfusion injury, hypertension, restenosis, arterial inflammation, heart failure, thrombosis and endothelial cell disorders. Specifically, the present invention identifies the differential expression of 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 and 6585 genes in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, and/or in response to manipulations relevant to cardiovascular disease. The present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition touch conditions. The invention also provides methods for identifying a compound capable of modulating cardiovascular disease. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/02571

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/00
US CL : 435/4; 514/866

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4; 514/866

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MILLS et al. Expression of TTK, a Novel Human Protein Kinase, Is Associated with Cell Proliferation. J. Biol. Chem. August 1992, Vol. 267, No. 22, pp. 16000-16006.	1, 2, 4
A	MILLS et al. (January 14, 1995) Acc. No. M86699, GenEmbl, Accessed June 2, 2003.	1, 2, 4
A	AH-KIM et al. Tumour necrosis factor alpha enhances the expression of hydroxylase lyase, cytoplasmic antiproteinase-2 and a dual specificity kinase TTK in human chondrocyte-like cells. Cytokine, February 2000, Vol. 12, No. 2, pp. 142-150.	1, 2, 4
A	KNOBLER et al. Shear-Induced platelet adhesion and aggregation on subendothelium are increased in diabetic patients. Thromb. Res. May 1998, Vol. 90, No. 4, pp. 181-190.	1, 2, 4
A	SANTOS et al. Participation of Tyrosine Phosphorylation in Cytoskeletal Reorganization, alpha IIB beta3 Integrin Receptor Activation, and Aspirin-Insensitive Mechanisms of Thrombin-Stimulated Human Platelets. Circulation, 2000, Vol. 102, pp. 1924-1930.	1, 2, 4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

18 June 2003 (18.06.2003)

Date of mailing of the international search report

18 AUG 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Valerie Bell-Harris for
Holly Schmitzer

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/02571

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Claims 1, 2, and 4 with respect to compound 1682

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/02571

Continuation of Item 4 of the first sheet:

The title of the invention is long (see PCT Rule 4.3) and the identification numbers do not provide any additional information as to the identity of the molecules used. Therefore, the title will be changed to the new title shown below.

New Title: Methods and Compositions for Treating Cardiovascular Disease.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1, 2, and 4, drawn to a method of identifying a compound capable of treating a cardiovascular disorder comprising assaying the ability of the compound to modulate the nucleic acid expression of compound 1682.

Groups 2-63, claim(s) 1, 2, and 4, drawn to a method of identifying a compound capable of treating a cardiovascular disorder comprising assaying the ability of the compound to modulate the nucleic acid expression or polypeptide activity of any one of compounds 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452, or 6585. If any of these groups are elected, Applicant must provide the elected compound number/SEQ ID NO:.

Group 64-126, claim(s) 3 and 5-13, drawn to a method of treating a cardiovascular disorder characterized by aberrant polypeptide activity or nucleic acid expression of any one of compounds 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 21656, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452, or 6585 by administering a modulator of the compound. If any of these groups are elected, Applicant must provide the elected compound number/SEQ ID NO:.

The inventions listed as Groups 1-126 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Pursuant to 37 C.F.R. § 1.475 (d), the ISA/US considers that where multiple products and methods are claimed, the main invention shall consist of the first invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first recited method of identifying a compound capable of treating a cardiovascular disorder comprising assaying the ability of the compound to modulate polypeptide activity or nucleic acid expression of compound 1682. Further, pursuant to 37 C.V.R. § 1.475 (d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The methods of Groups 1-63 involve the modulation of the expression and activity of polypeptides having different structures and completely different functions (compound 1682 is a protein kinase, compound 6169 is a methyl sterol oxidase, and compound 33216 is a fatty acid transport protein for example). Therefore, the methods would involve the testing of different modulators having different structures and functions and the methods would have completely different starting points, method steps and results. Applicants must pay appropriate fees for a search of each of the other compounds.

The methods of Groups 64-126 involve the treatment of a wide variety of disorders (see claim 10 for example) using modulators of polypeptides having completely different structures and functions. For example, compound 1682 is a kinase indicated as involved in platelet reactivity in diabetic patients and suggested for use in thrombosis whereas compound 6169 is a fatty acid transport protein involved in sterol biosynthesis and suggested for use in atherosclerosis and compound 18036 is a protease involved in hypoxia

INTERNATIONAL SEARCH REPORT

PCT/US03/02571

induced cell injury. Moreover, the different compounds are expressed in different tissues. Therefore, the modulators used in the methods of treatment would have different structures and functions and would be used to treat different diseases. Applicants must pay appropriate fees for a search of each of the compounds.

Continuation of B. FIELDS SEARCHED Item 3:

STN (Bioscience), EAST (all databases), sequence search, search terms: dual specificity kinase, TTK, cardiovascular, coronary, cardiac, diabetes, platelets, inventor search.